VOL. 32 SEPTEMBER 1956 NO. 9

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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CEREBROVASCULAR DISEASE WITH AGING

Transcription of a Panel Meeting

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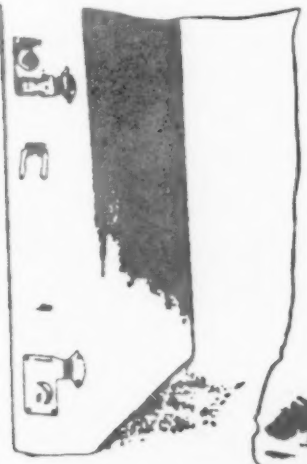

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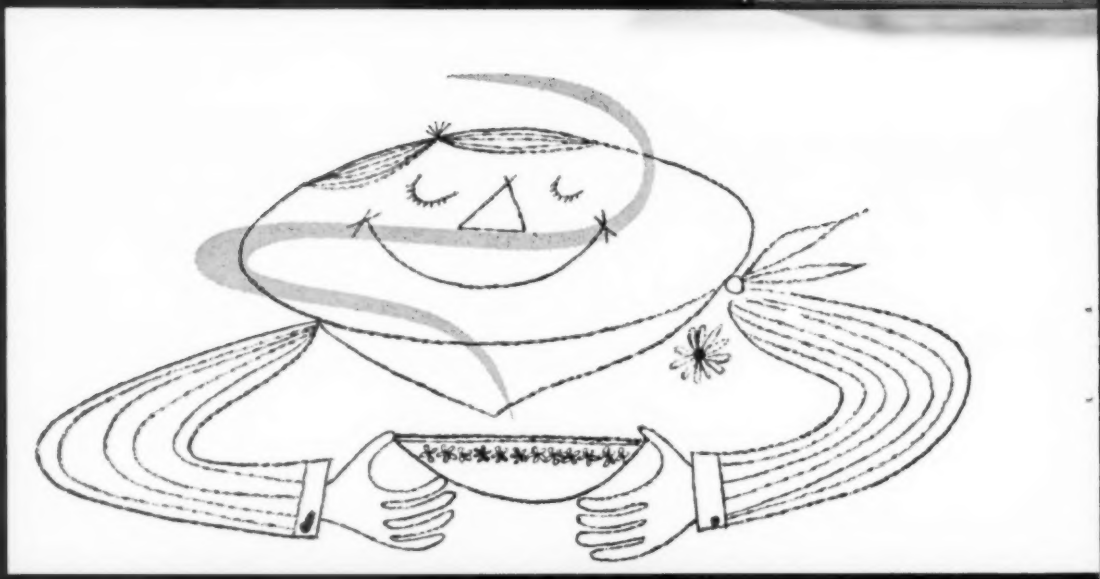

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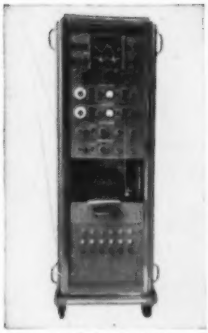

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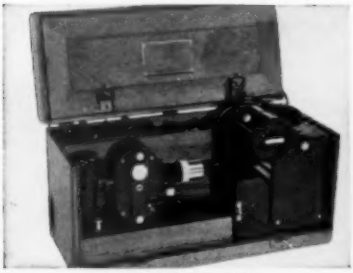

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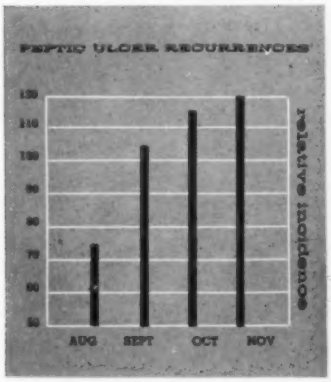

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $6.50. All other countries $7.50. Single copies 75c.
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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 32, NO. 9 SEPTEMBER 1956

EMOTIONAL AND PSYCHIATRIC PROBLEMS OF AGING*

FRANCIS J. BRACELAND

Psychiatrist-in-Chief, Institute of Living, Hartford, Conn.
President, American Psychiatric Association (1956)

SINCE the days of antiquity, old age has been a preferential theme of writers and philosophers. Its rewards, no less than its penalties, have been told in the literature of successive ages.

"Old age, on tiptoe, lays her jeweled hand
Lightly in mine. Come tread a stately measure,
Most gracious partner, nobly poised and bland."

These, the gracious words of Santayana, convey each man's hopes for his declining years. More often, however, it is as Hazlitt saw it:

"The young are prodigal of life from a superabundance of it, the old are tenacious on the same score, because they have little left, and cannot enjoy even what remains of it."

* Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 19, 1955.

The ability to enjoy what remains of life—this is a uniquely personal problem growing larger in scope now that longevity is the lot of the many rather than the few. It is also a major social problem, due to changing age distributions, the complexity of modern life with its personal and collective dangers, and even the mobile family structure itself. Only too often the senior citizen finds himself exiled from the green pastures of yesteryear to a gray sort of no-man's-land—alone, misunderstood and misunderstanding. The problem is major, too, in the field of medicine: how to deal with the aging human organism so that, despite chronic aberrations of one kind or another, harmonious integration proceeds until the end.

In few, if any, branches of psychiatry are the biological, social, psychological and pathological factors so sensitively attuned as they are in the emotional and mental disorders of old age. Physiologically, there occurs during aging a gradual impairment of homeostatic capacities along with degenerative tissue changes. Emotional pressures in themselves play a part in the breakdown of homeostasis and old age is a time of major stress for many people. The stress, unique in the experience of the individual, entails strenuous adaptive efforts—these in the face of waning physical and mental capacities. One by one the props of individual security vanish. The body image is distorted and the whole physical machine begins to sputter. The satisfactions of work and independence are largely evanescent and the individual feels impoverished in a purposeless, hectic world. Companions of a lifetime take their departure and the imminence of decay and death is not to be denied. Many people, even those exempt from the usual social and economic problems of aging, are unable to face this with equanimity. The rebellion that ensues may be expressed in ways that aggravate an already precarious position.

Senescence, it has been said, is as much a cultural artifact as it is a biological phenomenon.[1] Socio-economic pressures and frustrations weigh heavily upon the aged as they struggle vainly to retain roles beyond their competence or denied them for other and sometimes flimsy reasons. Sources of gratification evaporate, yet personality needs are as strong as ever: they flow through channels cut long before and involve the same offensive and defensive maneuvers. The rigidity traditionally equated with old age is, in part, the expression of the need to maintain a world that used to be—a world in which self-esteem, satis-

faction and relative mastery of the environment occurred at least some of the time. Inflexibility, a rigid life routine, is a defense against anxiety. It permits a denial or a warding off of threats, real and fancied, and makes possible an adaptation of sorts.

Frustration, disappointment, insecurity, organic impairment—all give rise to anxiety and each reinforces the other. Unless the personality retains sufficient integration to cope with the difficulties of aging and enough compensations are available to make up for the inevitable losses, reactive or endogenous morbid behavior may readily appear. Shorn of prestige, bereft of the old landmarks to adaptation, the aging individual is prone to distort the environment in which he lives. The environment does not take kindly to this. Intolerance begets intolerance and the social climate may actually become as inimical as the individual has feared or has imagined it to be. As his problems increase, emotional stress pyramids and becomes continuous. This chronic burden hastens senile deterioration. It compounds the handicap of memory defect and many times sets the stage for psychotic symptomatology. In a setting of impaired ego organization and fragmented defenses, strong instinctual drives escape repression and give rise to regressive behavior.

Our contemporary culture, which places a premium on youth, mobility and change, detours or demolishes impediments to movement. The aging person, whether or not he is aging with difficulty, is felt to be somewhat of a drag, and so he feels himself as a rule. He senses the hostility and fear aroused in others by the evidences of senescence. The tendency to respond with anxiety and hostility to the effects of aging and the problems of aged persons is almost universal. Sensitive to this, the senescent neither accepts it nor the fact of his decrepitude with philosophic indifference. Instead he feels angry and resentful. In order to achieve mastery, he often tries to exploit his position. The result may be importunate and demanding behavior, a querulous complaining, or a retreat to quiet martyrdom and hypochondriacal distortion. None of these responses may assume such proportions as to incapacitate the individual or those who may have to cope with him. They may simply mean a slow vicious circle of misery as everyone marks time for the approaching end. However, in some cases the impact goes far beyond even this sad *dénouement*. The stress imposed from within and without may open the flood gates so that the anxiety of the present merges with that of the past and major psychiatric illness ensues.

That functional mental illness is a frequent development of old age is a relatively recent observation. In the past any serious deviations displayed in senescence carried the burden of the inevitable. They were almost invariably ascribed to organic changes, cerebral arteriosclerosis providing the most convenient pigeon-hole for any psychosis displayed by a person past the age of 60. We know today that cerebral arteriosclerosis is a normal component of the aging process and that, while it may lead to an organic psychosis, it does so relatively infrequently and even then psychological and extracerebral somatic factors may be of considerable importance. Furthermore, the gravity of the mental symptoms and the severity of brain damage are not well correlated.

With the increased longevity of the population there has been for some time a sharp rise in the number of older patients admitted to mental hospitals. This is a development which continues to evoke dismay. However, the dismay is now tempered by the observation that in a sizable proportion of cases the conditions which force original hospitalization are comparatively benign. Organic psychoses do comprise an important segment of the problem in geriatric psychiatry, but by no means do they preempt the field. More manic-depressives now survive to have further attacks in senescence; and more persons reach old age so harried by emotional problems and their accumulated anxieties that only a mild degree of brain damage or even some other physical deviation may set off a psychotic reaction. At the same time, a substantial proportion of our older patients are people whose histories reveal no previous difficulties, but rather good performance throughout life. It has taken a series of frustrations, situational difficulties and deprivations of various kinds to build up sufficient anxiety to produce a psychotic reaction.

Affective psychosis occurs for the first time in old age much more frequently than was formerly suspected and, as in affective psychosis in other periods of life, the prognosis for the immediate attack is good. Whether we approve of it or not, it is apparent that electroshock therapy has achieved some of its best results in this group and the introduction of the new relaxants makes it possible to treat older patients in larger numbers than ever dreamed of before. The hazards are greatly reduced and, as O'Connell[2] has pointed out, even when the physical condition of the patient leaves something to be desired, the

risk of treatment must be balanced against the misery of a long mental illness.

Affective disorder of old age and senile dementia, in which there is intellectual deterioration, confusion and disorganization of the personality, are distinct clinical entities and differential diagnosis is extremely important for the clinician. Affective psychosis is a treatable disorder and, if not recognized, death by suicide or from increased liability to intercurrent infections may remove a salvageable human being. In most of the affective disorders of old age a depressive syndrome occurs. There is usually agitation with delusions of guilt and unworthiness, paranoid ideas consonant with mood, impaired appetite and sleep, and hypochondriacal complaints. Intellectual functions are retained and, though recent memory may seem grossly affected, this is often a superficial phenomenon based on the morbid preoccupations of the patient. There may also be highly atypical symptoms in these cases. Anxiety, aversion, hypochondriasis and even compulsive symptoms may be so prominent that the depressive mood disorder is inconspicuous.

In some patients who develop an affective psychosis for the first time in old age, a vulnerability to affective disorder has remained latent until the biological and psychological stress of aging has brought it to expression. The role of stress is often quite evident. This stress may take the shape of bereavement or some other major change in circumstances, or it may consist of physical trauma. Retirement from active work often antedates the illness. This bears out the thesis that one of the greatest sources of gratification in life is work and achievement, and that its loss may have a tremendous psychological impact. Particularly the person whose whole life has revolved around work and activity feels worthless and in the way when he has nothing to do.

In some cases, however, the illness seems to be engrafted on personality features of long standing. Anxiety-proneness, instability, mood fluctuations, self-centeredness, sensitivity and suspiciousness provide an excellent terrain for the development of an endogenous disorder. Conflicts carried over from earlier life are easily reactivated in old age. Particularly susceptible to depression in later years are personalities with rigid, stubborn, overconscientious and meticulous attitudes. The increasing physical and mental handicaps feed the anxiety of individuals who are basically insecure. They see no way out of the impasse and are overburdened with the aggressive impulses evoked by their fears

of decay and death. Depression and suicidal propensities then come to the surface.

Neurotic behavior in senescence is usually a continuation of previous, though less conspicuous, inadequacy. In fact, as Cameron[3] reminds us, qualities that previously brought success in life may hinder adjustment to a passive and subordinate role. However, there are other neurotic reactions which appear entirely out of the blue; such reactions frequently conceal an endogenous psychotic reaction which may become more severe if treatment is directed to the neurosis only. The same is true of incongruous new patterns of behavior in neurotic subjects. Beneath the scrambled symptomatology there sometimes lurks a depressive illness.

It is important to distinguish between endogenous depression and depression in the setting of cerebral disease. In the endogenous type, onset is fairly rapid. In the organic disorder, on the other hand, the history reveals a slow insidious onset in which impairment of memory and grasp, disorientation, emotional thinking and deterioration are prominent, and the depressive symptoms discontinuous, fragmentary and shallow.

Less frequent, though still not uncommon, is the development in later life of a paranoid psychosis, with primary delusions and hallucinations in clear consciousness and in the setting of a well preserved personality. The elderly female is more prone to this reaction than the male and defects of vision and hearing are present in about one-quarter of the cases. The clinical picture resembles that of paranoid disorder in middle life, but it has in addition features derived from the insecurity, loneliness and fears of the senescent. It also demonstrates the patient's attempts to solve the problem of aging and death by contriving a world in which it is possible to live out infantile strivings. Though prognosis for recovery from this disorder is poor, an evolution toward dementia is not the rule. The illness does not change its character with the passage of time.

Since paranoid symptoms are frequent in other kinds of mental disease in later life, especially in affective disorders, the importance of differential diagnosis is obvious. In affective disorder the delusions are depressive in coloring and their severity is consonant with depth of depression. In paraphrenia, on the other hand, there may be little affective resonance and, despite delusions of persecution marked by

noisy, aggressive behavior, affective response is inadequate or incongruous. The mean age of these patients tends to be higher than that of patients with affective psychosis and longevity more extended. Depressive illness carries a mortality that increases with age, in addition to the immediate dangers from suicide, inanition and exhaustion.

Functional psychoses of late onset are often ushered in by physical deficits. Physical illness, of which the patient may be unaware, may underlie an overt depression, just as overt physical symptoms may cover a depression. Inanition is particularly common in the aging population, especially among those who are living alone. Impairment of health and nutrition lowers the threshold for tolerance to anxiety, reinforces the impact of situational stress, and clears the way for the resurgence of unsolved conflicts. When general health and nutrition are improved, some patients recover spontaneously and some come along with the aid of simple psychotherapy. Many others, however, achieve recovery or significant improvement only after receiving electroshock treatment.

The enlarged experience with the psychiatric disorders of senescence has done much to shake the belief that older patients are poor subjects for intensive psychiatric effort. Working with these patients is neither as difficult nor as futile as tradition would have it. The presence of brain pathology does not mean that the case is hopeless, nor does major psychotic symptomatology mean organic disorder. It may just as well mean toxic psychosis, which is largely benign, or it may mean endogenous affective disorder or a reactive state, both of which are treatable.

In instituting a program of treatment, it is important to evaluate the early signs correctly. The task is often difficult because of the intimate relationship of organic and psychogenic processes. Furthermore, in old age disease processes have different rules and different courses from those in earlier life for, as Stieglitz[4] has indicated, causative factors are more endogenous, diffuse and cumulative. Precise diagnosis may be elusive, but active and energetic treatment is worth while in all cases.

The results of the interaction of a depressive illness and the effects of cerebral impairment are often complex. Moreover, the apathy which may be found in a depressive illness in senescence may suggest dementia. Some of these difficulties are resolved by a trial of physical methods of treatment. It is a common experience to find that electroshock removes certain features that were attributed to organic defect. Hence, arteriosclerosis and senile damage do not automatically exclude

the possibility of some degree of recovery in response to physical treatment. In this connection, the favorable effects of chlorpromazine on psychomotor over-activity of any variety and of reserpine on the mood and nervous symptoms of elderly hypertensives warrant attention. Trials in progress in clinical psychiatry may well add these promising drugs to the growing armamentarium of treatment in geriatrics.

For many senescents, however, physical methods of treatment provide only a partial answer and psychotherapeutic measures should be first considered. Any therapeutic program should be based on all aspects of the aging process. Doctors in general practice should never minimize the importance of treating even minor physical deviations in view of the ease with which inconspicuous factors tip the balance toward abnormal behavior. They would do well to recognize also that a wise combination of medical treatment and psychotherapy of a supportive type often yields unexpectedly good results. The goal of psychotherapy should be to restore emotional security and a sense of personal dignity in the individual.

In the behavior disorders of the aged, Goldfarb[5] has done especially interesting work with psychotherapy practiced in brief sessions (5-15 minutes) as widely spaced as possible. He uses a motivational approach designed to reorganize behavior along lines which the individual found useful in the past. In an approach such as this, it is essential to promote pleasurable interests, one of which is the patient's feeling that he is understood and appreciated by somebody—the doctor—and another, at least in some patients, the capacity to derive pleasure from struggle with, and a sense of mastery over, a powerful parent figure—again the doctor. Goldfarb is impressed with the frequency, in aged emotionally ill persons, of a long-standing attitude of joylessness, or of physical suffering, which has been used in an attempt to master the environment. He tries to help these patients feel that they have mastered him and won him to their service. In this way he fosters the illusion that all-embracing parental care and protection are continuously available. It is his experience that psychotherapy which offers support and fosters dependence is useful in many cases, even when chronic brain damage is present. In his words:

> ". . . man's chief environment is man, and even where pain and cerebral damage contribute to behavior disorder, the reaction may respond to change in the personal climate. One such change

is the development of personal relationships which relieve guilt, permit free expression of emotion, decrease fear and anger, and enhance the sense of worth."

So it is that the growth of experience and knowledge in geriatric psychiatry, together with current research on many fronts, bodes well for the solution of at least some of the many problems that confront us in this field. A better understanding of the biology of aging is of vital importance.

In addition to the biological and medical approaches to old age and its problems, research on stress must be continued and expanded. More pointed attention to measures which will reduce the emotional strains of later years is imperative. Simply as a bulwark against a flood of psychotic reactions in senescence, the provision of adequate social security and of a more agreeable social climate ranks high on the agenda. There must be concerted efforts to assure reasonably good physical health and vigor in later life and to provide opportunities for satisfying activities and relationships, the lack of which is particularly adverse to mental health. Compulsive retirement at a certain calendar age is as harmful to the individual as it is socially and economically wasteful. There should be a change rather than a termination of activities. Generally speaking, what is needed is a socially more responsible attitude to the old, together with better coordinated medical services and more adequate geriatric services.

The medical profession can never afford to forget how closely related are the phenomena of normal and pathological aging, how indistinct is their line of demarcation, and how easily, under the influence of a wide variety of factors, one may be transformed into the other.[6] If this is done, it will do much to dispel the fear of institutions which, no matter how ornate, still have the aroma of the poorhouse to the elderly. Regimentation and the loss of individuality associated with large institutions, so familiar in Dickens' novels, Symons[7] tells us, are an actuality to old people. Gitelson[8] puts it well when he says:

"Knowing that the old ones are really insecure and anxious the physician will lend them his own strength, not with a pat on the back and a wordy reassurance, but by the living fact of his willingness to stand by and help in every reasonable way. . . . There should be no talk about inferiority feelings, no talk about compensatory devices, no talk about anxiety. No jargon of

any sort is necessary. One must simply understand how the old person feels and conduct oneself with due consideration for the validity of these feelings."

We have been prodigal of manpower, wisdom and experience and it is time that we resurveyed the situation. It would be wise for us to keep in mind Cicero's injunction that intelligence and reflection and judgment reside in old men and, if there had been none of them, no states could exist at all.

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ANESTHESIA IN THE AGED*

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Introduction

A discussion of anesthesia in the aged will have little meaning unless it is understood that no hard and fast generalizations concerning anesthetic agents or methods in geriatric practice are possible. The inference must not be drawn that all elderly patients above the "geriatric" age whether it be 60, 70 or 80 are necessarily best anesthetized in the same specific way. The fundamental principles of good anesthesia apply to these patients as to all others. However, it is true that some patients in the older age groups are so brittle that even a gentle breeze of anesthetic gas or vapor seems to be a dangerous stress. This presentation must, therefore, be concerned with problems presented to the anesthesiologist *more frequently* in aged than in younger patients.

Some of the problems that must be solved in satisfactory anesthetic management of aging patients have to do with the physiological derangements and clinical illnesses which have been detailed in other presentations during this Graduate Fortnight on Problems of Aging. These disturbances of normal function may be of considerable importance when one adds to the picture the powerful and depressant action of the anesthetic agents. If it is possible to generalize at all one can state that aged patients appear to have a diminished ability to detoxify or eliminate potent anesthetic and sedative drugs. Furthermore, they appear to tolerate anesthetic procedures in a response range more limited than that of younger patients. These statements are meant to suggest that the major disturbances of anesthesia for the aged patients are only quantitatively different from those of younger subjects. This is an oversimplification but a basically correct one.

It has been observed repeatedly that the effects of premedicant drugs upon aged patients are more pronounced than they are in younger

* Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 18, 1955.

patients.[1] The former are apt to suffer depression of ventilation and circulation when opiates or synthetic narcotics are used in the usual dosages. The doses of these drugs must be reduced to something between one third and one half of the usual therapeutic range if they are to be used at all. There is considerable question whether the narcotics for premedication are valuable or even safe for aged patients. Since secretion production in the airway is not as much of a problem as it is in younger patients, belladonna drugs are given in smaller doses than usual. There has been controversy as to the relative merits of atropine and scopolamine in geriatric practice. It is quite unusual in our experience to note the delirium commonly ascribed to scopolamine. Delirium is not only rare but it is most apt to occur only in association with intense pain. It is difficult to document but it has been stated that elderly patients tend to be somewhat philosophical about events in the latter years. This has struck some so forcefully that the selection of regional anesthesia in the fully conscious state has been regarded as both physiologically sounder and psychologically satisfactory for these patients.[2]

Other aspects of the preparation of elderly patients are of interest and significance to the anesthesiologist. It is not pertinent in this discussion to review all the elements of care directed at restoring cardiovascular function, ventilation, renal function, and other important physiological activities to a status as near normal as possible. These are self evident and are more properly the concern of the internist. However, one important aspect of this phase of preoperative preparation is frequently overlooked. The internist and the anesthesiologist do not always provide the maximum safeguards for an elderly patient or one with heart disease who may not be elderly. This deficiency is related to the occasional failure to appreciate a total problem. The anesthesiologist does not always inform the internist of the precise action of his drugs or his procedures upon a given patient and what further risk may be superimposed by anesthesia under these circumstances. The internist, on the other hand, is not always able to inform the anesthesiologist of how much functional disability may be expected in a patient with a diseased heart. The pious hope to provide "adequate oxygen and avoid a fall in blood pressure" is somewhat academic. The avoidance of anoxia and circulatory depression is basic to good clinical anesthetic care.

The preoperative preparation of elderly patients for major surgical procedures includes the important matter of insuring an adequate blood

volume. If one uses the standard reference of body weight with a reasonable allowance for the aging process, the blood volume in proportion to body weight is lower in many elderly people than it is in young adults.[3] A circulating volume defect prior to the induction of anesthesia becomes increasingly important since the elderly patient is less able to effect circulatory compensatory shifts provoked by the action of anesthetic agents and surgical procedures. Circulatory morbidity and mortality will, therefore, be increased if the circulating blood volume deficits are not properly corrected prior to the beginning of anesthesia and if significant losses of blood during operation are not corrected as they occur.

The Effects of Anesthesia

In properly managed anesthesia, the mortality from the anesthetics need not be disproportionate nor a clinical deterrent to the performance of needed surgery in aged people. Turville and Dripps[4] found, at the University of Pennsylvania, that the hospital mortality was 4.9 per cent in 974 patients over age 70. This included death from all causes although the actual death rate from anesthesia was not specified. At the University of Iowa in 478 operations upon patients of the age of 80 or above, Ziffren[5] found an overall mortality of 15.1 per cent. This series also did not separate the anesthetic mortality from other causes of death. Bosch, Islami, Tan and Beling[6] reported a mortality in elective procedures of 8.8 per cent and an increase in mortality in emergency procedures to 17.4 per cent. McDermott and Papper[7] reported a total mortality of 4.3 per cent in the anesthetic management of 254 patients with fractures of the hip whose average age was 64.9 years. Mortality included any death that occurred in the postoperative period regardless of how long it occurred after actual operation. There were all told 12 deaths. Three of these patients died of pulmonary embolism in the pre-anticoagulant period, four died in congestive failure, one death occurred with terminal cirrhosis of the liver, three died of pneumonitis, and the cause of death in the last was not clear. It appeared definite that well conducted anesthesia and skillful operation did not add materially to the danger of death in this group of patients. It was difficult to assess the part played by anesthesia in causing these deaths. If anesthesia were implicated at all it probably did not account in any important way for more than one and at most two of these 12 deaths. The low mortality in

this series could not be attributed to the specific type of anesthesia since most forms of anesthesia were employed during the period from 1930 to 1950. The principle of very light general anesthesia was followed in most instances.

Cole[8] stated that "The elderly patient is more susceptible to the ill effects of hypoxia and anoxia, largely because of vascular changes in the brain, heart, etc. For this reason the anesthetic in elderly patients becomes a very important part of the operation." This statement of Cole's suggests that the physiological control of the anesthesia, rather than the specific agent itself, is more important in the ultimate welfare of the elderly patient. This is not peculiar to the elderly patient but is also a reasonable analysis of anesthetic management in any patient. Cole went on to point out in the discussion of specific agents, that in his judgment cyclopropane was adequate and safe and that nitrous oxide and ethylene were not desirable because they do not permit sufficient oxygenation. The criticism of the use of nitrous oxide and ethylene suggests that these agents must always be administered with inadequate oxygen concentrations. These anoxic mixtures are not necessary nor are they practiced in good anesthetic management. In fact, with adequate oxygen, these non-potent gases are among the best of agents for general anesthesia.

In the studies reported by Turville and Dripps[4] in 974 patients, spinal anesthesia was given 448 times, thiopental 206, cyclopropane 193, ether 66, and some form of regional anesthesia 150. A large number of the patients given spinal anesthesia developed hypotension; 33 per cent of the patients who had spinal anesthesia had falls in blood pressure to the level of 60 mm. Hg systolic pressure in normotensive patients or less than one half the original pressure in hypertensive patients. This magnitude of fall in pressure occurred in only 12 per cent of those given general anesthesia. Although one would suppose that falls in blood pressure are highly undesirable in aged patients, Turville and Dripps found that there were relatively few complications of hypotension. It did not appear that hypotension of this degree was responsible for a significant increase in the incidence of myocardial infarction or renal vascular change.

One cannot consider in detail the pharmacology of each anesthetic agent and its suitability for the aged patients. A few pertinent observations, however, can be made for application to these patients.

Types of Anesthesia

1. *Ether:* There has been much discussion of the advantages and disadvantages of ether in many circumstances, including its suitability for the care of the aged. It seems to the present author that an important point is frequently overlooked in this type of discussion. Among the major disadvantages of ether anesthesia are those due to the fact that it is a potent agent. The establishment of deep anesthesia is very easy to accomplish in aged patients with relatively small doses. The profound refractory depression of the circulation is particularly evident with ether overdosage. The first sign of overdosage may be sudden circulatory collapse. Elderly subjects do not usually develop a preliminary tachycardia and tachypnea as ether anesthesia deepens. Time is apparently telescoped for these subjects and the effects of profound etherization become evident with much smaller quantities and much earlier in the course of anesthesia. It is not inferred, however, that ether cannot be used satisfactorily in the aged. It can and has been used to good advantage provided that only the lightest plane of surgical anesthesia or the stage of analgesia is utilized. The important point is that the anesthetic depth must be light with this agent and its administration skillfully performed, realizing that very small quantities can achieve relatively profound depths of anesthesia.

2. *Cyclopropane:* This is an agent which also evokes controversy in the field of geriatrics. Opponents of its use cite the fact that its potential for inciting cardiac irritability makes it unsuitable for elderly patients who may have cardiac arrhythmias. The ease of depression of ventilation with cyclopropane is also cited as a disadvantage in that oxygenation of the blood, despite the high concentration of oxygen in the inhaled atmosphere, may be difficult. More particularly, the excretion of carbon dioxide may be impaired resulting in respiratory acidosis during anesthesia and postanesthetic hypotension and ventricular arrhythmias. These criticisms and objections are valid but, as in the case of ether, they may be overcome by the assistance or control of ventilation and the utilization of the lightest planes of general anesthesia.

Emphasis has been made twice about the value of light anesthesia for elderly patients. It should also be added that it is usually possible to provide good working conditions for the surgeon even with the lightest planes of anesthesia. When relaxation is not totally adequate

under these conditions, a satisfactory surgical field can be achieved more safely by the use of a relaxant than the deepening of anesthesia. Considerable care must be exercised when relaxants are employed to avoid the possibility of overdose of the anesthetic since the "natural" protection of laryngospasm against the potent agents may be eliminated.

3. *The Nonpotent Gases:* Ethylene and nitrous oxide may be considered together since they cannot provide the deepest planes of surgical anesthesia. In aged patients, however, it is usually possible to achieve surgical anesthesia of a satisfactory depth with either one. Ethylene is enough more potent than nitrous oxide so that a somewhat deeper plane of anesthesia can be achieved than with nitrous oxide. Ethylene is explosive and nitrous oxide is not. As far as is known, neither agent has any intrinsic toxic effect upon any organ system in the presence of adequate oxygenation and efficient ventilation. It is important at this point to lay to rest one of the myths in the discussion of anesthesia for the elderly patient. It is frequently stated that ethylene and nitrous oxide are unsuitable or, in fact, dangerous because of the anoxia they produce. If these agents are used for young, robust patients without supplementation this criticism is valid. In the aged patient, however, these agents are more than satisfactory in the majority of patients because anesthesia of satisfactory depth can be achieved with an adequate supply of oxygen and without demonstrable toxicity. In fact, in the modern practice of general anesthesia in geriatrics, ethylene and nitrous oxide should be considered the agents of choice for elderly patients provided an adequate concentration of oxygen is used (more than 25 per cent).

4. *Intravenous Anesthesia:* Intravenous anesthetic agents produce general anesthesia with all the attendant advantages and disadvantages of general narcosis. There are several drugs in current use. Most of them are rapidly acting barbiturates. In elderly patients doses as small as 50 mg. of Pentothal Sodium or Surital Sodium may produce significant depression of respiration and circulation. These drugs, if used in the elderly, must be given with extreme caution in dilutions which permit the injection of precisely determined doses (0.5 to 2.5 per cent) as a basal hypnotic for the maintenance of anesthesia with nitrous oxide oxygen or ethylene and oxygen. They must not be used in aged patients as the sole anesthetic drug.

5. *Rectal Anesthesia:* It is generally advised that the use of Avertin

and Pentothal by rectum be avoided in elderly patients because in the doses satisfactory for production of basal narcosis considerable hypotension may develop. This generalization seems to be a rational and safe one and yet does not jibe totally with actual clinical experiences. The cases reported by McDermott and Papper[7] include the use of Avertin in their earlier case reports. This agent in elderly patients did not appear to increase the mortality despite the fact that it increased the incidence of hypotension.

6. *Local Anesthetic Agents:* If local or regional anesthesia is satisfactory for the surgeon's requirement and for the personality of the patient, they appear to offer maximum safety. A major hazard in the use of these agents is the matter of total dose. In this respect the local anesthetics are the same as the general anesthetics and the narcotics. Elderly patients do not tolerate the doses used for younger patients. Therefore, smaller concentrations of local drugs and smaller total doses should be both satisfactory and safer in the aged.

7. *Spinal Anesthesia:* Spinal anesthesia has been used and advocated by many. The major disadvantages of this method are the relatively high instance of hypotension and the difficulty of assuring effective correction once it has occurred. It has been pointed out above, that hypotension does not per se appear to increase the mortality rate.

It must also be mentioned that postoperative psychosis is among the important complications of both spinal and general anesthesia in aged patients. Seven per cent of the patients reported by Turville and Dripps[4] were irrational after operation. They do not state whether this irrational period was prolonged or whether it could be considered psychotic. It has also been an observation of the clinicians who watch with interest the more subtle changes after surgical procedures that "grandfather is not the same after his prostatectomy." One can only speculate whether the precipitation of irrational behavior or even a psychotic episode might not be associated with cerebral anoxia due to the effect of spinal or general anesthesia. Perhaps the sclerotic vessels of the elderly reduce the margin of safety compared to that of younger adults. It must be reemphasized that this is only speculative. Further observations along these lines might be quite fruitful.

8. *The Relaxants:* The relaxants are not so valuable in the management of aged patients as they are in those with greater muscle power and greater "resistance" to the effects of anesthetic agents. However, the

employment of relaxants appears to be rational as a substitute for added depth of anesthesia should this be necessary for elderly patients. It is of particular importance to be certain that prolonged respiratory depression does not ensue with the use of these agents. Conservative dose administration is essential and the preservation of spontaneous breathing or the frequent recourse to testing for the return of spontaneous respiration when controlled respiration is used is mandatory.

Position

Most anesthetized patients tolerate unusual positions on the operating table poorly. Therefore, when postural change is required for the completion of surgical operation, it is essential that movements be made slowly, gradually, and gently to minimize the call for circulatory compensation in which these patients show deficiencies.

In the postoperative period, sedative drugs must be used in small doses or omitted entirely to avoid the side effects produced by narcotics which are apt to be more harmful in the aged than in younger patients. Aspirin and phenobarbital (not an analgesic) are frequently satisfactory in achieving comfort in the postoperative period.

The point of view expressed in this presentation can best be summarized by Rink's[9] advice to the anesthesiologist whose responsibility includes the care of the aged, "When faced with a wet and slippery road on a dark night, a first class driver does not alter his techniques in any essential way. He merely redoubles his normal safeguards and precautions. He avoids rapid acceleration and braking, but he reaches his destination very nearly as quickly and safely as he does under good conditions."

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A CONTROLLED STUDY OF RESERPINE IN THE TREATMENT OF MENTAL ILLNESS*

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THIS paper is a report of the results of an attempt to establish a double blind study of the effects of reserpine (Serpasil)† when this drug was employed in the course of treatment of a series of 50 patients (15 male and 35 female) at the New York Hospital-Westchester Division. This hospital is a voluntary private hospital for the treatment of patients suffering from mental and emotional illness. The patients included in this study had been under treatment at this hospital for varying periods of time and for varying degrees of illness. At some stage of their illness reserpine was used in the course of therapy of each of the 50 patients. Some of these patients had already received electroshock or sub-shock insulin therapy and, in one instance, a lobotomy had been performed (in another institution) prior to the use of reserpine in this series. Following the course of reserpine further adjunctive therapies were employed in some instances. All of the patients in this series also received psychotherapy and the planned program therapies of the hospital.

The 50 patients were selected for treatment without specific regard to the presenting symptomatology, age or diagnosis. Their ages ranged from 15 years to 78 years and the duration of reported symptomatology or mental or emotional illness, prior to but directly related to their hospitalization at the New York Hospital-Westchester Division, ranged from eight days to 19 years.

Anxiety, depression and restlessness were the most frequently recorded symptoms just prior to the initiation of reserpine therapy. In the following order, but with lessening frequency, symptoms of agita-

* Presented by Dr. Prout at the combined meeting of the Section on Neurology and Psychiatry with the New York Neurological Society, at The New York Academy of Medicine, December 13, 1955. Manuscript received December 1955.

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† The product used in this study was Serpasil, generously supplied by the Ciba Pharmaceutical Products, Inc.

tion, insomnia, obsessive-compulsive phenomena, overactivity, impulsiveness, apathy, indifference, negativism and frustration were recorded prior to reserpine medication.

Placebo tablets and intramuscular placebo preparations, which were physically indistinguishable from their equivalent and counterpart dosage, were obtained. The reserpine and reserpine placebos were administered in alternating and identical courses according to a prearranged schedule which included the strength and duration of the course, so that it was by chance only whether a given patient began treatment with the medication or with the placebo. Neither the patients nor the members of the staff, who were in immediate supervisory capacities with the patients, were cognizant of whether the medication itself or the placebo was being administered.

Throughout the course of this experiment all of the 50 patients continued with their regular program of activities except when contraindicated by marked physical side effects of the medication or unrelated physical symptoms. Furthermore, no other adjunctive somatic therapy was prescribed throughout this same period for these patients except for an occasional and temporary use of sedation. Psychotherapy was continued at regular intervals by the physicians in charge of the patients.

Detailed observations were recorded for from three to seven day periods prior to the drug or placebo administration in order to establish a base line for each patient. Recorded observations were then continued throughout the period of drug or placebo administration. These included records of blood pressure, pulse, respiration, temperature, weight and sleep. Prepared nursing records provided a day by day description of behavioral changes and physical complaints. A weekly evaluation, using the Psychiatric Rating Scale of Malamud and Sands* was completed on each patient throughout the study period by the physicians immediately in charge of each of the patients, in addition to the regular hospital record progress notes. Thus detailed records of physiological and psychological changes were obtained and, for comparison and evaluation, each physician was limited to a standard form and the same descriptive terms. Three dosage schedules were arranged:

1. Low dosage (received by 25 patients): An initial intramuscular injection of 3.5 mg. was followed by the daily administration of 1.5 mg. orally for a period of at least three weeks.

* Malamud, W. and Sands, S. L. A revision of the psychiatric rating scale, *Amer. J. Psychiat.* *104*:231-37, 1947-1948.

2. Moderate dosage (received by 13 patients): For the first week, 5 to 10 mg. were given daily and orally.

For the second week 5 mg. orally, daily. Then, for periods with a total average duration of six weeks, 2½ to 5 mg. daily, orally.

3. High dosage (received by 12 patients): Intramuscular injections of 5 mg., twice daily, augmented by an additional 5 mg., intramuscularly, each day, to a maximum dosage of 30 mg.

Oral administration of 15 mg. was then substituted for the intramuscular injections and the dosage gradually reduced to from 5 to 10 mg. daily, which was maintained for periods averaging seven weeks.

The blind technique of administration was considered successful and satisfactory.

The most frequently encountered complaints, due to side effects of the drug, were lassitude, fatigue or drowsiness in varying degrees of intensity. Actually the side effects ranged from a mild headache or flushing of the face to quite severe manifestations which are usually associated with Parkinson's disease, such as mask-like facies, tremors, muscular rigidity, and the typical cogwheel phenomenon. Nasal stuffiness, dry mucous membranes, edema of the face and of the extremities, dizziness, vomiting or diarrhea were observed. Some drop in blood pressure and bradycardia were almost invariable consequences of reserpine medication. Temperature findings were consistently within normal range.

The severity of observed side effects was, in general, in direct ratio to the size of the dosage employed. They were classified as minimal, moderate and marked, to indicate gradations of severity. The side effects observed in the 25 patients on the low dosage schedules were mainly of minimal character with a few presenting moderately severe symptoms. The 13 patients on moderate dosage schedule still presented side effects of minimal severity for the most part but two of the 13 had marked reactions. On the other hand, six of the 12 patients receiving the high dosage presented moderately severe side effects and five had marked reactions.

All of the observed side effects were found to be alleviated and reversible, in a matter of a few hours to a few days, upon reduction or discontinuance of the drug.

In determining the results, this study was so designed that the observed patients' reactions could be rated or classified as improved,

TABLE I—SIDE EFFECTS

Dosage Schedule	*Number of Cases*	*Minimal*	*Moderate*	*Marked*
Low	25	20	5	0
Moderate	13	9	2	2
High	12	1	6	5

markedly improved or unimproved. A further category of sustained improvement was tabulated for those patients who did not relapse upon withdrawal of medication.

These ratings could be established in four categories:

1. General behavior; this included appetite, sleep, appearance, socialization and work ability.

2. Manifestations of anxiety; these were measured by an assessment of feeling, motor activity, responsiveness and aggressiveness.

3. General mood and display of affect.

4. Mental trend and ability to communicate verbally; this included mental content, associations, thought processes, awareness and recollection.

The patient must have been regarded as at least improved or better in each of the afore-mentioned categories to be considered as markedly improved.

The observed results of the various dosage schedules were, surprisingly enough, almost identical in their psychological effects, although the side effects increased proportionately with the higher dosage. Six patients who had been on the high dosage had to be discontinued from the study when they developed severe parkinsonism within four to seven days after the initial dose. One of these patients developed a severe urticarial rash. Within the limits of the periods of observation, no more satisfactory results were obtained in the group treated for a total of six or eight weeks than for those treated for three weeks.

Of the 50 patients in this series, 50 per cent were improved and an additional 16 per cent were markedly improved for a total of 66 per cent improved, or markedly improved, on reserpine as compared with 30 per cent who were improved on placebo. This is a significant difference using the X^2 formula, as the probability was point 5 per cent.

TABLE II—RESULTS ON PLACEBO

Dosage Schedule	*Number of Cases*	*Improved*	*Markedly Improved*	*Unimproved*
Low	25	36%	0	64%
Moderate	13	23%	0	77%
High	12	25%	0	75%
Total	50	30%	0	70%

TABLE III—RESULTS ON RESERPINE (SERPASIL)

Dosage Schedule	*Number of Cases*	*Improved*	*Markedly Improved*	*Unimproved*	*Sustained Improvement*
Low	25	72%	16%	28%	36%
Moderate	13	61%	15%	39%	8%
High	12	58%	17%	42%	8%
Total	50	66%	16%	34%	22%

In 11 patients, or 22 per cent of this series, the improvement was sustained after cessation of medication and they were able to leave the hospital without further adjunctive therapy. Twenty-two, or about 44 per cent of the patients in this series have received electric shock therapy, other drug therapy, and one underwent a lobotomy following their treatment with reserpine.

The results of therapy with reserpine were then investigated in terms of diagnostic reaction types.

Seventeen of the 50 patients were regarded as suffering from some type of schizophrenia. Eleven of these 17 were classified as catatonic, three paranoid, one hebephrenic, and two as simple type. One of the two classified as schizophrenia, simple type, had undergone a lobotomy prior to her admission to this hospital. She failed to show any response to reserpine therapy. Nine of the 11 catatonic patients improved with reserpine and six of these nine sustained their improvement. Two of the three paranoid schizophrenic patients improved with reserpine but failed to maintain the improvement. The one hebephrenic type also improved but did not sustain the improvement. One of the two, diagnosed as simple type, improved and sustained the improvement.

TABLE IV—RESULTS IN SCHIZOPHRENIC GROUP

Type of Schizo.	*Number of Cases*	*Improved on Placebo*	*Sustained Improved on Placebo*	*Improv. on Reserpine (Serpasil)*	*Sustained Improv. on Reserpine (Serpasil)*
Catatonic	11	3	0	9	6
Paranoid	3	2	0	2	0
Hebephrenic	1	0	0	1	0
Simple	2	0	0	1	1
Total	17	5	0	13	8

The observed improvements, in the schizophrenic group, appeared to be not alone in the area of anxiety, as has been postulated by other authors, but was noticeable in other symptom categories and appeared to be an across-the-board improvement. It was impossible to determine from our study which symptom complaint responded first to the therapeutic effect of the drug. Five of the 17 schizophrenic patients had also improved on placebo medication.

Eight of the 50 patients had been classified as suffering from a manic-depressive illness of circular type. Six of these received reserpine while they were in the depressive phase. There was no significant difference in the response of these six patients to the reserpine than to placebos. Four of the patients showed some improvement in mood while receiving placebos while three responded similarly to reserpine. All of these patients relapsed upon withdrawal of medication except one, and four of the six later required electroshock therapy. The one patient, who did maintain improvement, had shown marked improvement on both placebo and reserpine. The response of the patients in the depressed phase was disappointing and tends to confirm the reports of others that reserpine is not particularly effective in the psychotic depressions. Two of the eight patients were in the manic phase. Both of these revealed marked improvement on reserpine and one maintained the improvement after withdrawal of the medication.

The manic-depressive mixed type and involutional melancholias were grouped together under the classification of agitated depressions. Sixteen of the 50 patients were included in this diagnostic grouping. Eight of the 16 showed improvement while receiving reserpine as

TABLE V—SUMMARY OF RESULTS

Diagnostic Grouping	*Average Age*	*Number of Cases*	*Improved on Placebo*	*Improv. on Reserpine (Serpasil)*	*Sustained Impr.*	*Later EST*
M.D. circ. (depress.)	43	6	4	3	1	4
M.D. circ. (manic)	51	2	1	2	1	0
Agit. Dep.	60	16	3	8	2	13
Psychoneur.	52	5	2	5	0	2
Schizo.	31	17	5	13	7	2
Elderly	73	4	0	2	0	1
Total	47	50	15	33	11	22

compared with three on placebo, and only two maintained the improvement upon withdrawal of the drug. Thirteen of the 16 required electroshock therapy at a later date. The observed improvement noted in those who did respond to reserpine was in the form of a reduction in restlessness, anxiety, and the general behavior improved somewhat as compared to the response to placebos.

Of the five patients considered to belong in the diagnostic grouping of psychoneurosis, all showed some improvement with reserpine and two with placebo. None of these patients maintained the improvement upon withdrawal of the drug and one of the five did considerably better on placebo than on reserpine. This group was prone to marked side effects which they tolerated poorly.

Four patients suffering from senile psychosis or psychosis with arteriosclerosis were classified as the elderly group. The major response in these four lay in that they became easier to manage and less noisy. None revealed any change in trend and again severe side effects were poorly tolerated and made the patients more vulnerable to accidents and stasis problems.

SUMMARY

1. This study suggests that clinical change is not dependent upon the size of the dose of reserpine although the side effects are.

2. The suggested effective therapeutic range lies between 2 and 10 mg. daily.

3. The majority of improvement is observed by the end of the first three weeks following initiation of treatment.

4. It appeared from this study that four weeks seem to be an adequate period in which to ascertain whether reserpine is to be effective.

5. There appeared to be a significant benefit to patients in the schizophrenic group. Those schizophrenic patients who did show marked improvement did so in all four categories.

6. In the manic-depressive circular group some improvement appeared in the manic phase but no benefit was noted in the depressive phase.

7. Only transient benefit was observed in psychoneurotic patients, with a tendency to relapse upon discontinuance of medication.

8. Reserpine appeared to be of some value in the treatment of about one-half of the agitated depressions but only while on the medication.

9. The placebo disguise appeared to have been effective in this study.

10. The side effects of the drug were reversible.

11. Reserpine is not to be regarded as a cure but as another valuable addition to the armamentarium of the psychiatrist in making the patient more amenable to psychotherapy or program therapies.

PLASMA CLOT SUTURE OF TENDONS: EXPERIMENTAL STUDY*

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TENDON surgery in the hand has always been plagued by the problem of fibrosis. Many techniques have been devised to combat this problem. Tendons have been surrounded by foreign material to prevent fibrosis only to find that fibrosis is thereby increased.[1-4] Ingenious methods have been devised to form new tendon sheaths by means of metal inserts (personal communications from J. Milgram) and plastic inserts;[5] these have not solved the problem. Bunnell[6] has developed a technique whereby the suture material can be removed from the repaired tendon entirely after partial healing. Others have tried the systemic approach: cortisone[7] and hydrocortisone[8] have been given, all to no avail.

There are many today who feel that the most effective treatment for tendon lacerations is tendon grafting, the grafts permitting suture in areas outside of "No man's land", that difficult area between the distal palmar crease and the proximal interphalangeal joint.[9]

Similar problems have been encountered by neurosurgeons in suturing nerves. A method for nerve suture which gives the least reaction and is most physiologic is the plasma clot technique, largely developed and refined by Tarlov.[10]

This method has been found so effective by neurosurgeons, it was applied in this study to the suture of tendons in rabbits.

METHOD

The technique of the plasma clot suture is described in Dr. I. M. Tarlov's book,[10] "Plasma Clot Suture of Peripheral Nerves and Nerve

* Presented before the Section on Orthopedic Surgery at The New York Academy of Medicine, April 25, 1955. Manuscript received March 1956.

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This investigation was supported by the Committee on Research of the Jewish Hospital of Brooklyn.

Roots." This technique was followed in the present work.

Fifteen rabbits were used in these experiments. Their average weight was nine pounds and the average age was one year. The nutrition of all the animals was good.

The rabbits were divided into three series of five rabbits each. In one series the tendons were sutured by means of 5-0 arterial silk with a curved number nine atraumatic needle; in the second series the tendons were sutured with tantalum wire, size .003 inches in diameter, also using an atraumatic curved needle, and in the third series the plasma clot technique was used. The method of tendon suture with silk and tantalum was the classical back and forth suture with one knot.

The animals were operated on under intravenous Nembutal anesthesia supplemented by cone ether if needed. The plantar flexor tendon of the rabbits corresponding to the tendo achillis in the human was utilized. This tendon was used knowing that the Achilles tendon does not have a true sheath and, in this respect, differs from the flexor tendons of the human hand and foot. This made no difference to the experiment since we were looking only for differences in local reaction.

The hair of the rabbits was clipped in the area overlying the plantar flexor tendons. The tendons were sectioned transversely using a sharp razor blade. All surgery was done with sterile technique. The procedures were performed by the same persons.

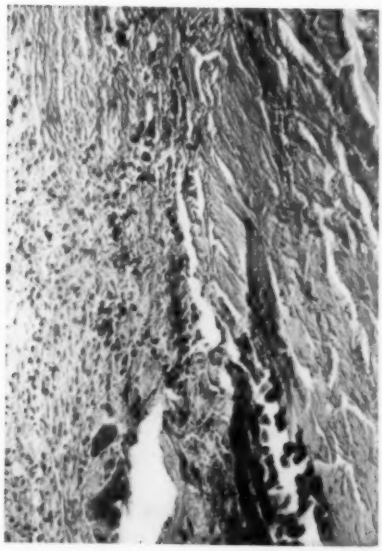
Plaster of paris long leg casts were used to immobilize the limbs after suturing. Intramuscular injections of penicillin were given to each rabbit for two days after surgery. No infections were encountered.

The animals in the different groups were sacrificed in two, three, and four week intervals. The suture line and an adjacent inch of tendon were removed, fixed, sectioned and stained with hematoxylin and eosin and then examined histologically.

Gross and Microscopic Examination

During the gross examination attention was paid to the ease with which the incision could be opened, the density and quantity of adhesions between the skin and the peritendinous tissue, the quantity of fibrous tissue surrounding the tendon and the condition of the suture line.

In the gross findings it was found that the silk suture caused a marked reaction, the tendon was adherent to the superficial fascia and there was proliferation of fibrous tissue about it.



(X350)

Fig. 1—Photomicrograph of silk sutured tendon examined at 21 days shows silk suture with surrounding cellular reaction.

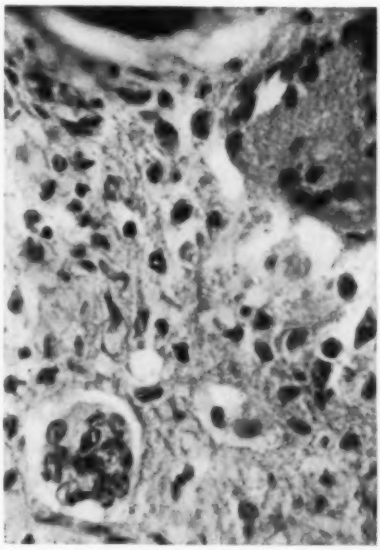


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Fig. 2—Photomicrograph of silk sutured tendon examined at 21 days shows cellular reaction consisting chiefly of mononuclear and foreign body giant cells.

The tendon sutured by tantalum wire showed less reaction. However, all tendons so sutured were somewhat adherent posteriorly.

The tendon sutured by the plasma clot technique showed the least gross reaction. In all areas it could be separated from the surrounding tissue with comparative ease.

Histologic examination of the specimens verified the gross evaluation. All tendons showed union. The histologic preparations presented are representative of each group of sutures.

Tendons sutured by silk showed a marked cellular reaction (Figs. 1 and 2). Those sutured by tantalum showed less reaction (Figs. 3 and 4). Tendons sutured by the plasma clot technique showed practically no reaction (Figs. 5 and 6).

These findings were confirmed by Dr. David Grayzel, Director of the Department of Pathology of the Jewish Hospital of Brooklyn. He was given all of the slides without knowledge of the technique of

(X350)

Fig. 3

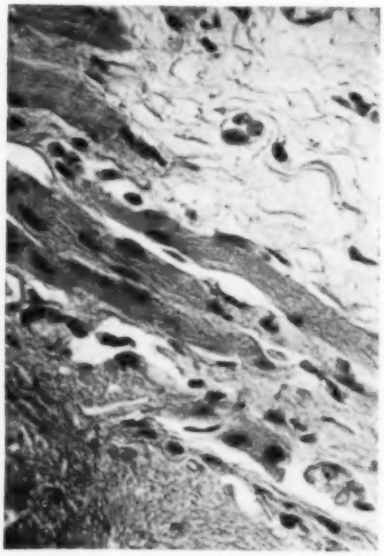

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Fig. 4

Photomicrographs of tantalum sutured tendon examined at 21 days shows only mild round cell reaction. There are no foreign body giant cells.

suture. Interestingly enough, he was able to separate the slides sharply into three groups, the plasma clot group showing uniformly little or no tissue reaction at the suture site.

Discussion

One criticism of the plasma clot method is that strong enough fixation cannot be obtained with it, that the suture line will pull apart during the first few days. This is not so if adequate immobilization of the limb is maintained. In using plasma clot for tendon suture clinically a pull-out suture at a distance[6] can be utilized to relieve longitudinal tension. The plasma clot would then prevent side to side forces from disrupting the suture line. Moreover, because the clot might act as a tendon sheath, as is the case in nerve suture where the clot acts as a nerve sheath, scar tissue encroachment on the suture line probably would be prevented.

(X350)

Fig. 5

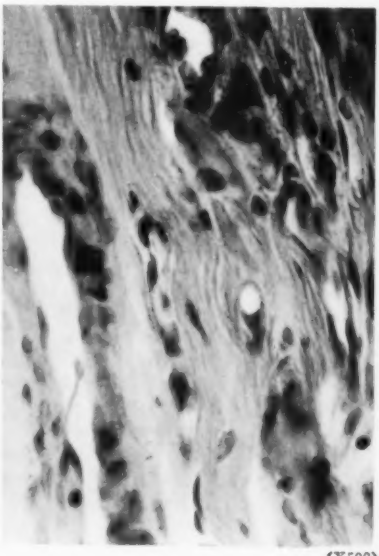

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Fig. 6

Photomicrographs of plasma clot sutured tendon examined at 21 days. Shows no cellular reaction in the tendon suture line. There is some bleeding noted in the surrounding tissues.

From this experiment, the plasma clot technique appears to be an effective method in combating fibrosis in tendon repair; this method has already proved its worth in nerve suture. Since the combined problems of tendon and nerve severance often occur, this one method might be used for both problems simplifying the operative procedure.

It should, of course, be noted that the plasma clot technique is an exacting one and must be modified to work in such close quarters as the hand. The latex molds now employed are cumbersome. Molds can be formed of nearby fat and muscle as has been done in nerve work on the face. In the hand, the fascial compartments themselves can be made to act as molds.

Future plans for further investigation of this problem include studies on the tensile strength of the suture line and experiments on the flexor tendons of dogs, rather than rabbits, which tendons more closely simulate flexor tendons of the human hand.

Note: I am indebted to Dr. I. M. Tarlov for his helpful advice on technical problems and his constant encouragement and constructive criticism. I also wish to acknowledge the assistance of Dr. Phillip Zeitler. He was called into active duty in the Army of the United States during this study and his valuable help was lost.

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CEREBROVASCULAR DISEASE WITH AGING

*Transcription of a Panel Meeting**

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*Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 18, 1955.

MODERATOR IRVING S. WRIGHT: Our panel is going to proceed on a very informal basis. We shall have one person discuss a question briefly and then see if we can stir up a little controversy and see what current thinking may be as it is expressed by other members of the panel. In addition we welcome questions from the floor. The members of this evening's panel are qualified not only by appointment but they have all spent some years being concerned with the problem which is to engage us this evening.

This major problem has been sadly neglected in the past but in the last year or two has come more to the forefront of medicine. In 1952 approximately 170,000 people died with cerebralvascular diseases in this country. It is true that many of them were elderly. However, more than 44,000 of them were in the productive age group under 65 years of age. This represents an enormous loss of productivity to the country. In addition it is estimated that approximately 1,800,000 people alive today in the United States have suffered from some manifestations of cerebral vascular disease. Many of them are not only incapacitated themselves but in addition they require the aid, often full time, of from one to three or four additional people, which again represents an enormous loss to our community life in this country. There are many thousands confined for long periods in various private, municipal, state and veterans hospitals unable to care for themselves as the result of these diseases. Many more thousands are in nursing homes or the homes of their families where they constitute a heavy burden. It is not necessary for me to go into this in greater detail since I am sure that this audience fully recognizes the gravity of the problem.

The question is, what are we going to do about it? In order to do anything we must begin by trying to understand it. An attempt has been made in the last several years to ask questions, to stimulate people, who have been mildly or moderately interested in the past, to intensify their efforts. We also hope to attract the interest of many younger physicians and research workers in this major problem.

We will deal first with questions about the anatomy and pathogenesis. Dr. Adams, what is the extent of the collateral circulation between the various cerebral arteries?

DR. RAYMOND D. ADAMS: I should say that the collateral circulation is more amply provided for than one would expect from the fact that an occlusion of an artery leads to softening of the brain. Of course, it is

well known that the circle of Willis is an arrangement of arteries for providing collateral blood supply to the brain, in case of occlusion of a vertebral, basilar, or carotid artery. A few observations that we have made would suggest that there is a complex series of meningeal anastomoses on the surface of the brain which connect the major branches of adjacent cerebral and cerebellar arteries. These begin to operate when any one of the major cerebral arteries becomes occluded distal to the circle of Willis. Lastly, at the capillary level there is an extremely rich collateral circulation.

One might then answer the question by saying that there are three series of collateral vessels in the human brain. Upon occlusion of any major cerebral artery probably two or all three of these anastomotic systems begin to work. The result is that arterial occlusion usually produces only a relative ischemia within any given territory of the brain and the area of softening that results is always much smaller than the extent of the circulation of the vessel that is occluded. Nevertheless, when ischemia exceeds a certain degree, tissue viability is no longer possible and the stroke which has resulted leaves a more or less permanent residue of neurologic defect.

MODERATOR WRIGHT: *Dr. Merritt, do you have additional comments to make in reference to this?*

DR. H. HOUSTON MERRITT: Studies that have been made on patients who have had operative procedures for cerebral aneurysms have shown that the collateral circulation sometimes travels via routes that we would hardly expect. Angiographic studies made on patients who have had their internal carotid artery ligated show that in some cases the blood gets to the brain by way of the ophthalmic artery. Dr. Lester Mount described a case in which he ligated the internal carotid in the neck and within the cranial cavity. Angiograms a year later indicated that blood was getting to the middle cerebral and anterior cerebral arteries by way of the middle meningeal, which, of course, arises from the external carotid.

MODERATOR WRIGHT: *Why were these ligations done?*

DR. MERRITT: For the removal of aneurysms which had bled. I would like to add that in spite of terminal anastomoses mentioned by Dr. Adams, occlusion of a terminal branch of a vessel is more apt to cause death of tissue than occlusion of a large branch in a young person. In an elderly person where the vessels are sclerotic the chances of getting

normal restoration of circulation by accessory channels become greatly diminished.

MODERATOR WRIGHT: *Dr. Fazekas, do you have anything to add?*

DR. JOSEPH F. FAZEKAS: I have nothing to add.

MODERATOR WRIGHT: *Dr. Covalt?*

DR. DONALD A. COVALT: I would like to ask a question of one of the other members of the panel. In our work in cerebral palsy, we have had different time periods of anoxia cited as the cause of the changes or death of the nerve cells, particularly in a child. We have noted estimates ranging from 15 to 60 seconds and it would seem that there is some time relationship between duration of anoxia and the extent of brain cell recovery. I thought perhaps one of our panelists might discuss this.

MODERATOR WRIGHT: *Dr. Adams, how long do you think a nerve cell can be anoxic without death?*

DR. ADAMS: Experimental data would indicate that in the fetus anoxia may be withstood for a much longer time than in the postnatal period of life. Some of Dr. Fazekas' work has borne that out. In the child or adult there is fair reason to believe that a period of about six minutes of total circulatory arrest will invariably cause death of nerve cells. This time interval is not always reliable when estimated from clinical data, however, because one usually does not know in any given case how complete circulatory arrest was.

In conditions of cerebral vascular occlusion, however, a new set of factors is brought into action and tissue may survive a relative ischemia of far longer duration than would be possible in total circulatory arrest. As a matter of fact, no one knows how long a vessel may be occluded and then opened up without death of tissue. In the macaque it would seem from the work of Rasmussen that if an arterial occlusion is relieved within 45 to 60 minutes, there will be complete functional recovery and preservation of tissue. Such data are not available in humans.

MODERATOR WRIGHT: *Dr. Fazekas, your work has been quoted. Do you care to comment or defend yourself?*

DR. FAZEKAS: It is generally agreed that those brain areas with the highest metabolic requirements are most sensitive to either ischemia or hypoxia. As Dr. Adams has stated, the newborn animal (rat) can survive in an atmosphere of pure nitrogen for as long as 40 minutes presumably because of the low cerebral metabolic rate at this stage of development. With aging there is an increased cerebral metabolic rate and an increased

sensitivity to ischemia and hypoxia. The adult animal succumbs within one minute when exposed to an atmosphere of pure nitrogen. In subjects who have had cardiac arrest for periods of six minutes or longer, irreversible brain damage invariably results. At our institution we still have a patient who had cardiac arrest three years ago which was estimated to be of approximately six minutes' duration. Her physical condition is fine and temperature, vasomotor and respiratory centers are all functioning normally. She is, however, for all practical purposes completely decorticated. I think that from the available clinical and experimental data one can estimate that cortical cells become reversibly damaged after about six to eight minutes of complete ischemia and that lower centers are somewhat more resistant.

MODERATOR WRIGHT: *Dr. Merritt, we often hear controversy about whether there is such a thing as spasm of the cerebral vessels. I would like to open this general subject for discussion. The first question: Is the caliber of the cerebral blood vessels controlled by the nerves?*

DR. MERRITT: I believe that the evidence indicates that only the very large cerebral vessels have vasomotor nerves. The question of whether vasospasm can occur within the nervous system is one that cannot be settled clinically and is one that is very difficult for the pathologist to prove or disprove. We know that changes in the systemic circulation can cause insufficiency of the blood supply to the brain and in some instances relatively greater insufficiency to one vessel than to another and produce hemiplegia. We do not have any direct evidence to show that nerve stimuli can cause constriction of a cerebral vessel sufficient to produce an occlusion or a thrombosis of that vessel. We do know that the musculature of the vessels is quite irritable to chemical stimuli and that the injection of chemicals can cause the vessel to go into spasm but there is no evidence that stimulation of any of the nerve trunks produces spasms of the cerebral vessels.

MODERATOR WRIGHT: *Dr. Merritt, what do you think happens to the vessels supplying the brain when patients experience a series of episodes of numbness or transient paralysis in which they recover the function and a few hours later or the next day they have another episode involving the same area? They recover from that one but over a period of time continue to have these episodes and finally days, weeks, or months later develop a permanent paralysis. What do you think is the explanation for this if it is not cerebrovascular spasm?*

DR. MERRITT: That is a difficult question to answer. It is one which we have a little better chance of answering now than we did some years ago when we did not realize how frequently insufficiency of a large trunk occurred. We did not realize, for instance, that sclerosis and thrombosis of the internal common carotid was a fairly common event. In such cases a transient reduction in the systemic circulation could unfavorably influence the circulation to the brain, and transient paralytic phenomena could develop because the circulation to the hemisphere that has the sclerotic artery suffers more than the other. When the transient disturbance of the general circulation clears up, the symptoms disappear. I think that this explanation probably accounts for only a small percentage of the patients that Dr. Wright has in mind. Patients may have numbness of one hand which may last for only a few minutes and then after several such episodes they may develop a complete hemiplegia. It is difficult to understand the mechanism of these attacks. You might postulate that there has been an interference with the circulation in terminal branches of the middle cerebral artery which supplies small portions of the brain adjacent to the arm area of the cortex. The function of the arm area of the cortex may be disturbed by edema in this region. If the thrombus extends backward or a new thrombus forms in a larger portion of the vessel, then permanent paralytic phenomenon develops. But this is also only an hypothesis that is used to avoid the hypothesis of spasm.

MODERATOR WRIGHT: *Dr. Adams, would you like to comment on this hypothesis versus any other?*

DR. ADAMS: I must admit that I still have a rather open mind on this problem. I have no doubt but what transitory disturbances of the brain occur, and not infrequently. One fairly obvious explanation for a single transitory ischemic attack might be that the plugged vessel and the softening that resulted therefrom lay next to but not right within a vital nervous structure. In other words, if the corticospinal tract were affected it might recover in minutes, hours or days because it lay in the periphery of the zone supplied by the occluded artery. Not infrequently a person will have a hemiplegia of a few hours' duration, with complete recovery and later, at postmortem examination there is a small area of softening near the corticospinal tract but not destroying it.

Quite a different problem, however, is posed by the type of case where 50 or 60 ischemic cerebral attacks will follow one another, with

complete or nearly complete clearing of symptoms in the intervals. Finally there will be a permanent hemiplegia. I don't believe this can be understood at the present time nor has the phenomenon been placed on a sound physiological basis. I am hopeful, if enough human cases are studied carefully, clinically and pathologically, that certain hypotheses can be worked out and tested in humans. It is surprising how many of these cases have diseases of the carotid and the vertebral-basilar arteries. My impression is that a local circulatory insufficiency is always operative but that an element of vascular spasm related to segmental arterial *disease* cannot yet be excluded. However, I would reject the notion that spasm could be the sole explanation of such states.

MODERATOR WRIGHT: *Do you know of instances when under surgical observation vessels have contracted without the injection of drugs?*

DR. ADAMS: I have known of cases where the carotid artery was exposed in the neck or at the base of the brain and where upon manipulation of the vessel or injury of it a very strong spasm was induced so that the vessel could not be cannulated.

MODERATOR WRIGHT: *Then you have to assume that there are contractile fibers capable of doing this?*

DR. ADAMS: Yes, there is a strong muscular coat in these vessels except in the most severely atherosclerotic ones in which it may have degenerated.

MODERATOR WRIGHT: Dr. Fazekas.

DR. FAZEKAS: I would agree that the neurogenic influence on vasomotor tone of cerebral vessels is relatively weak and perhaps we should be glad that such is the case. The tone of cerebral vessels has been shown to respond readily to changes in carbon dioxide tension. With an increase in carbon dioxide tension, there is a decrease in cerebral vascular resistance and a marked increase in the rate of cerebral blood flow. On the other hand, a decrease of carbon dioxide tension, as occurs with hyperventilation or following the injection of aminophylline, results in an increase in cerebrovascular resistance and a very significant decrease in the rate of cerebral blood flow. These latter findings indicate rather conclusively that cerebral vessels have the capacity to undergo some degree of constriction.

MODERATOR WRIGHT: *Dr. Covalt, do you have any comments on this?*

DR. COVALT: Only to point out that it is necessary to take a careful history on patients who have already had a cerebral accident. Many of

these people will not have told their doctors about it. It means thorough interrogation of the family and to me it is an exciting piece of research that must be done because I think the incidence of these prodromal affairs is higher than we might think. If we can discover the cause of it then perhaps we may find a remedy which will reduce the incidence of the critical number of cerebral accidents we are seeing today.

DR. FAZEKAS: May we conclude then, everyone is in agreement that stellate ganglion block is without effect as far as cerebral vessels are concerned and that the procedure is not particularly beneficial?

MODERATOR WRIGHT: *Why do you think it is not? As a matter of fact, we have not concluded whether the vessels are capable of spasm or not. We have two different opinions.*

DR. FAZEKAS: I think Dr. Merritt and I both agreed that the influence of the nerves on the cerebral vessels was relatively slight.

DR. MERRITT: Relatively slight but the effect of chemicals could be very great. Carbon dioxide, for instance, is capable of producing significant changes in the cerebral circulation.

DR. FAZEKAS: Right!

MODERATOR WRIGHT: *How was the effect operative if the nerve control is relatively slight?*

DR. FAZEKAS: The direct effect of changes in acid-base balance.

MODERATOR WRIGHT: *On the muscle-nerve endings?*

DR. FAZEKAS: Directly on the muscle, I think.

MODERATOR WRIGHT: *I am trying to pin these points down as they arise. In considering the stellate ganglion block, we are getting ahead of ourselves a little but while we are talking about nerve influence we might as well discuss this procedure which has been advocated as a therapeutic measure. You appear to have strong feelings about this, Doctor Fazekas. Will you let us know what your feelings are and what is your evidence?*

DR. FAZEKAS: I think it is extremely difficult in view of the variable history of patients with cerebralvascular disease to evaluate the efficacy of any procedure. Milliken studied the effects of stellate ganglion block in a fairly large number of subjects and came to the conclusion that the procedure was not beneficial. We have noted just as many dramatic recoveries in patients not subjected to stellate ganglion block as in those receiving such treatment. We, too, do not feel that the procedure is worth while.

MODERATOR WRIGHT: *Do you use stellate ganglion block on your*

service, Dr. Merritt?

DR. MERRITT: No. It is not used because our experience did not indicate that the course of patients treated by this method was any different from those who did not receive this therapy. As Dr. Fazekas has pointed out, all of the controlled studies, that is the studies in which one group of patients were treated by stellate block and another similar group were not, showed that the results were no different in the two groups. That has been true of all of the controlled studies. The favorable results have usually been reported by physicians who have treated all their patients with this method and then compared their results with their previous clinical experience.

MODERATOR WRIGHT: *Any comments, Dr. Adams?*

DR. ADAMS: No.

MODERATOR WRIGHT: *Dr. Covalt?*

DR. COVALT: Perhaps we see only the bad results of stellate ganglion block at our Institute. From what we see of the patients who have been treated with stellate ganglion block before they come to our Institute, there is no difference in their recovery than those who have not had a stellate ganglion block.

I might add we have one rather tragic case in the Institute now who has been rendered quite paretic following stellate ganglion blocks.

MODERATOR WRIGHT: *Let us now go back to more fundamental concepts and return to therapy later. Dr. Adams, do you think it can be said that age is a cause of cerebrovascular disease?*

DR. ADAMS: I would say there can be no doubt that aging is accompanied by a rising incidence of morbid changes in the arteries of the human brain. The figures which you yourself have presented attest to this fact. There are, however, many different vascular diseases of the brain arteries. I could list the following: atherosclerosis; calcification of the carotid and vertebral arteries; embolic occlusion of brain arteries by fibrin thrombi and atheromatous material and inflammatory clots; endarteritis obliterans sometimes loosely referred to as Buerger's disease and other types of arteritis; fibroelastic degeneration of large arteries, fusiform, globular and saccular aneurysms (probably two or three different processes involved here); hyaline arteriosclerosis; hyperplastic arteriolosclerosis; necrotizing arteriolar disease; Charcot-Bouchard aneurysm; capillary and pericapillary fibrosis; pseudocalcification, ferrugination of brain arteries and arterioles, and lastly, fibrosis, calcification, cyst forma-

tion and atheromatosis of the choroid plexuses. It seems unlikely that all of these diseases would have the same cause and the same mechanism. They differ morphologically and in distribution within the vascular system.

One subject that I think we might consider for the moment is whether or not any of these diseases are exclusively related to the aging process itself? I think I might summarize current opinion amongst pathologists by saying that there appear to be a number of changes that increase steadily from birth to the end of life. These have been studied quite systematically by Binswanger and Spielmeyer, Jacob, Heckel, Baker and by Gellerstedt. They have examined brains from patients of all ages who were supposed not to have had any disease of the central nervous system. They point out that the most consistent and progressive changes are alterations of the vessels due to loss of elasticity. The large vessels on the surface of the brain become wider and longer, more tortuous, more stiff, less collapsible. Under the microscope one can find that there is an alteration in the elastic tissue, interruptions of and a reduplication of the internal elastic lamina, a thinning of the muscular coat and some degree of replacement by fibrous connective tissue and in the smallest vessels, the capillaries and precapillaries, an increase in the reticular connective tissue in the adventitia. Also the choroid plexuses undergo fibrosis and calcification and many of the small vessels within the substance of basal ganglia and dentate nuclei undergo peculiar hyaline changes, and finally calcification or iron deposition. It seems remarkable to me that only a few attempts have been made to study these changes. Gellerstedt's monograph written in 1932 is probably the only thorough study of age changes in the vessels of the brain. His study may be criticized because one cannot be sure that his patients were all normal. He did not examine them himself and the clinical data are meager. There is still a need for a thorough clinical and neuropathological study utilizing the best and most modern techniques of histopathology. The vascular changes that I have mentioned which tend to correlate with age do not lead to occlusion of brain arteries or to any of the common vascular syndromes which can be recognized clinically. However, the possibility that these changes in the small vessels could be related to the progressive loss of brain weight with gradual outfall of cells and fibers and with senile plaques, Alzheimer fibrillary changes or any of the other commonplace changes in the senile brain, remains

unsettled. Gellerstedt himself suspected that the outfall of nerve cells, which tends to be rather irregular in the cerebral cortex, was due to the capillary fibrosis. Others have not been able to confirm this but it has not been studied very thoroughly. The possibility that molecular changes in the brain capillaries could impair capillary permeability and thereby interfere with the nutrition or with the removal of waste products is certainly an attractive hypothesis, but cannot be affirmed or refuted by the present day knowledge. The techniques of the microphysiologist and electron microscopist have never been applied systematically to this field and one would expect that much might be learned by these methods if they could be adapted to the study of brain vessels.

MODERATOR WRIGHT: Thank you very much. That is an interesting and stimulating approach and shows some of the directions we ought to go in the next few years.

Dr. Merritt, in your opinion, what is the relationship of intracranial pressure to systemic blood pressure?

DR. MERRITT: There is no direct relationship between intracranial pressure and systemic blood pressure. Patients with high arterial tension will have perfectly normal intracranial pressure unless there are other complicating factors. Intracranial pressure is directly related to venous pressure which of course is correlated with capillary pressure and not with arterial pressure. It is true, however, that some patients with a high degree of hypertension may have a slightly higher intracranial pressure than the patients with "normal" tension. Other factors probably play a part here, possibly small vascular lesions, possibly retention of certain toxic substances leading to cerebral edema. There is, however, no direct correlation between arterial tension and intracranial pressure.

MODERATOR WRIGHT: *Are there comments or disagreement on this? If not we will discuss the relative frequency of the various types of cerebrovascular lesions. I will ask Dr. Adams to summarize his experience and then we will compare it with that of other members of the panel.*

DR. MERRITT: May I speak to that first and Dr. Adams second because he will offer statistics based on a meticulous examination of necropsy material? I would like to give the commonly accepted opinion from the clinical viewpoint. Approximately 60 per cent, or a little less than two-thirds, of the patients that are admitted to the hospital with

a "stroke" have a cerebral infarct, which is usually attributed to an occlusion of the vessel by a thrombus, and are labeled cerebral thrombosis. About 25 per cent have an intracerebral hemorrhage and the other 15 per cent are divided between ruptured aneurysm and an embolic phenomenon. The latter is diagnosed clinically only when the examination discloses a source for an embolic phenomenon. These are the figures based on clinical impression. The figures will be somewhat different for necrospy controlled material because cerebral hemorrhage is a fatal disease and most of these cases will come to autopsy, whereas many of the patients with occlusive phenomena will recover and be discharged to die of something else later. The autopsy statistics are heavily weighted with hemorrhagic phenomena.

MODERATOR WRIGHT: *Dr. Adams has looked at this problem from a somewhat different viewpoint and I think we should hear his findings.*

DR. ADAMS: Actually, our figures are not far apart. It is true that hemorrhage is nearly always fatal in the first attack. We very seldom find old hemorrhages in the brain suggesting that the person has had a hemorrhage and then survived it for a period of time. About 20 to 25 per cent of the postmortem cases in which death is due to a vascular lesion of the brain, have a sizeable hemorrhage. The other 75 to 80 per cent of cases will be due to softenings, with a small number of cases of hypertensive encephalopathy, saccular aneurysm and venous thrombosis and so forth. Of the softenings, the pathologist can demonstrate a thrombus in an atherosclerotic vessel in a fair number of them, perhaps a third, and he can demonstrate an embolus blocking a vessel and causing infarction in about an equal number. So of the proven cases, embolism and major artery thrombosis will be about equally frequent in the old age population of large municipal hospitals. But there are always softenings, many of which are not immediately fatal for which we cannot find an explanation. It is on the basis of these cases that it has been suggested that vascular spasm operates. However, our impression is that if one examines the material with great care and if the neck vessels are dissected and thrombi and emboli searched for, there will be very few softenings of the brain for which one does not find a vascular occlusion.

DR. MERRITT: I would like to point out that Dr. Adams was able to pick up a number of embolic phenomena from his pathological studies that the clinicians missed on their examination of the cases.

Perhaps as clinicians become more alert to the problem, the discrepancy will become less evident.

MODERATOR WRIGHT: *I would also like to point out that the figures which are advanced in support of any ratio should be considered in the light of the institution from which they come. For instance, it is conceivable to me that a general hospital with a large and strong cardiac service will probably have a higher relative incidence of embolic phenomena than, for instance, a neurological institute or an institute for old people whose patients have died from cerebral vascular diseases. So, hemorrhage, thrombosis and embolism might change in their ratios depending on the importance of the various services in the hospitals. Is there any disagreement with that position?*

DR. MERRITT: No disagreement.

DR. ADAMS: It also varies with the attitude of the pathologists because they don't all agree on terminology. I was looking at the exhibit of brains in your lobby a few minutes ago, and note that specimen No. 20 is labeled as "brain hemorrhage." We would call that hemorrhagic infarct and look very hard for an embolus. You can see how if the pathologist were calling all such cases brain hemorrhages, his figures would be quite different than others.

MODERATOR WRIGHT: *Also, to belabor the point just a bit, it would depend on the thoroughness of the pathological department and this, in turn, may depend somewhat on its finances and the number of man hours that can be devoted to studying each brain. Is that correct?*

DR. ADAMS: Yes.

MODERATOR WRIGHT: *Is it not true that one of the weaknesses in our pathological investigations of nervous tissue in the past has been the need for the large number of sections of each brain required for thorough study and which few institutions can support?*

DR. ADAMS: Very few can. Just the number of hours it takes to work out the vascular system to look for vascular occlusions, to make maps of the lesions and obtain representative microscopic sections may be almost prohibitive.

MODERATOR WRIGHT: *Dr. Merritt, do you think a lumbar puncture should be performed in every case, or almost every case, or rarely?*

DR. MERRITT: The one test that will aid most to help differentiate between hemorrhage and thrombosis (or embolism) is lumbar puncture. For that reason lumbar puncture is of great diagnostic value. To

say that a lumbar puncture should be done routinely in patients with cerebral vascular accident, would be going a bit too far. Some patients are admitted to the hospital in extremis, obviously due to a large hemorrhage or thrombosis of a major arterial trunk and it is obvious that treatment will not be of any value. If a lumbar puncture were performed in such a case and the patient died within an hour or two, it might be thought that the procedure hastened the death. There is, of course, always the fear that the lumbar puncture may disturb intracranial relationships and add to the existing damage. Taking all things into consideration a diagnostic lumbar puncture should be performed in most cases because it will give valuable information that will serve as a guide in the treatment. In some cases it is not needed, either because the diagnosis is obvious or the circumstances are so grave that it is contraindicated.

MODERATOR WRIGHT: *Dr. Merritt, one more question in this regard: Have you personally seen death following lumbar puncture in this type of case, in which 10 cc. of fluid or less have been removed?*

DR. MERRITT: I have not seen death in any patient that I thought was due to a lumbar puncture. I have seen death occur within a number of hours after lumbar puncture but I thought the patients were going to die anyway.

MODERATOR WRIGHT: *Dr. Fazekas, what is the general policy on your service?*

DR. FAZEKAS: In our institution, whenever there is any question regarding diagnosis, a lumbar puncture is done. If we suspect that there is increased intracranial pressure a small caliber needle is used and only a small amount of fluid is withdrawn slowly. I have never seen herniation through the foramen or tentorium as the result of lumbar puncture when the procedure is done as indicated.

MODERATOR WRIGHT: *In asking this question, I would like to emphasize that we are now talking only about cerebral vascular cases and not people with meningitis or other infectious processes. Dr. Adams, what is your feeling about the lumbar puncture and have you ever seen a case of this type in which you would consider that death was due to lumbar puncture?*

DR. ADAMS: I feel much as Dr. Merritt does about it. We try not to let any procedure in medicine become routine. There are times when one has the impression that the lumbar puncture has made condi-

tions a little worse or at least has not helped either in diagnosis or in treatment. In hypertensive encephalopathy and occasionally in brain hemorrhage or a massive infarct, it may lead to the formation of a temporal or cerebellar pressure cone. In general I think that whenever the diagnosis is in doubt, that a lumbar puncture should be done and that one must decide on the most opportune time to do it, depending at least in part, upon the treatment program.

MODERATOR WRIGHT: *Dr. Covalt, do you have any comments to make?*

DR. COVALT: Only concerning rehabilitation. The differential diagnosis between a hemorrhage and a thrombosis is very important in helping to decide the time of starting rehabilitation treatment, about which we will talk later.

MODERATOR WRIGHT: My own experience in this regard covers civilian and army practice on fairly large services and I have been particularly interested in trying to trace down the probability of death or serious complications as the result of lumbar punctures done carefully, with withdrawal of 5 to 10 cc. of fluid but not large amounts, rapidly. So far I have not encountered any serious consequences and I do believe that in most cases, except in the very extreme ones that Dr. Merritt mentioned, lumbar puncture is a valuable diagnostic aid.

Now we come to the question of angiography. Dr. Merritt, what is your feeling about angiography?

DR. MERRITT: Angiography is of definite value in cases where the diagnosis of aneurysm or angiomatous malformation is entertained. Angiograms should not be done in patients with embolic or thrombotic lesions, because the information obtained as to the site of lesion is not of sufficient value to justify the risk involved.

MODERATOR WRIGHT: *Would you enlarge on the type of complications which you have seen as the result of angiography?*

DR. MERRITT: The complications are: spasm of the vessel as a result of irritative action of the dye and the puncture of the vessel with resulting ischemia of the cerebral hemisphere and contralateral hemiplegia. In the majority of cases this paralysis is temporary but sometimes it is permanent; convulsive seizures may occur also without paralysis; and in addition the artery may be lacerated, producing a hemorrhage into the neck. Usually this is not of great consequence and the hemorrhage can be stopped by a bandage but it is possible to tear the artery

so that serious hemorrhage will result. There have been cases reported where the intima of the vessel has been torn and the vessel later became thrombosed.

The relative incidence of these complications is low because angiography is usually performed in young people. Patients with cerebrovascular disease, outside of those with aneurysms, are usually middle aged or elderly and the state of their vessels is not as good as in young persons so that as a rule angiography is contraindicated in patients with a vascular lesion except in those cases where there is a good possibility that an aneurysm or angiomatous malformation is present and the findings will be of value in determining what mode of treatment should be carried out.

MODERATOR WRIGHT: *Dr. Adams, would you like to comment on this?*

DR. ADAMS: I think we have probably tentatively arrived at almost the same policy. We do not use angiography for the diagnosis of any type of vascular disease other than aneurysms or angiomas, if we suspect beforehand what we are dealing with. The reason that we have been reluctant to use it is the risk of increasing the damage,—hemiplegias, aphasia, death from hemorrhage into the neck with glottis edema, have occurred occasionally in our cases.

MODERATOR WRIGHT: *We will now comment on the usefulness of electroencephalographic tracings in the determination of cerebrovascular accidents or diseases. Dr. Merritt, would you like to comment on that?*

DR. MERRITT: There have been few studies of this problem. Electroencephalography has not been used as extensively in the diagnosis of cerebral vascular lesions as it has in brain tumors. Abnormalities in the electroencephalogram are usually found in patients with vascular lesions affecting the cerebral hemispheres. These changes usually improve with the passage of time almost independently of changes in the focal neurological signs. Repeated electroencephalograms are, therefore, of value in differentiating a tumor from a vascular lesion because the electroencephalographic changes usually become progressively worse in patients with a tumor.

MODERATOR WRIGHT: *Dr. Adams, comments?*

DR. ADAMS: I would only say that at our hospital, we have not learned to use the electroencephalogram intelligently. I would suppose

that if we used it in all cases early in the disease we might get helpful information that would enable us better to state the locale of the disease and better to follow it. I have been aided from time to time in cases where a definite cerebral lesion was demonstrated but was somewhat uncertain as to whether it was vascular or not. The gradual resolution of the electroencephalographic changes, i.e., the diminution of abnormality with passage of time tends to exclude a tumor.

MODERATOR WRIGHT: *I think the time has come for us to discuss therapy. Dr. Fazekas will you open this discussion by commenting on the use of so-called vasodilators. Are they of any value in the management of the patients with cerebrovascular disease? If so, do you have suggestions as to which ones might be preferred?*

DR. FAZEKAS: I don't know whether cerebrovasodilators are of any value in the symptomatic treatment of patients with cerebrovascular disease. As stated before, it is extremely difficult to determine the efficacy of these agents in a condition that changes spontaneously from day to day, as does the course of patients with cerebrothrombosis. Most vasodilating agents currently available cause general vasodilatation, a reduction in blood pressure, and hence no changes in rate of total cerebral blood flow.

MODERATOR WRIGHT: *You include nicotinic acid?*

DR. FAZEKAS: Yes. Probably the most effective cerebral vasodilator is carbon dioxide, 5 per cent. Its inhalation results in a very significant increase in the rate of cerebral blood flow and decrease in cerebral vascular resistance. However, it has not been used in the acute case to any great extent. Milliken has recently published a report on the effects of inhalation of carbon dioxide on the course of patients with acute cerebral thrombosis. These patients inhaled 5 per cent carbon dioxide for periods ranging from five to ten minutes each hour over a 48-hour period. After carefully analyzing his data, Milliken could not say conclusively that even this potent cerebral vasodilator was effective in influencing the course of these patients. So as far as vasodilating agents are concerned, I look at them with extreme skepticism and believe that those which reduce blood pressure are of little value.

MODERATOR WRIGHT: *If you wish to use carbon dioxide because that is the only one that stands the test in any scientific way, is it possible for the patient to accomplish this by rebreathing, using a paper bag or plastic bag instead of setting up elaborate apparatus of the carbon*

dioxide inhalating machine?

DR. FAZEKAS: That is perfectly possible, to rebreathe from a bag for periods of time up to five minutes and during that time get effective cerebrovascular dilatation. Once the rebreathing stops the effect is over.

MODERATOR WRIGHT: *Dr. Adams!*

DR. ADAMS: I would say that we use several vasodilators because we like to do something that is rational.

MODERATOR WRIGHT: Dr. Fazekas says it is not rational.

DR. ADAMS: They dilate the blood vessels, get more blood into the infarcted areas. That seems sensible, though I am sure that nature has thought of this before we have gotten around to it since the vessels all around the infarct are usually fully dilated.

MODERATOR WRIGHT: *What about hypotensive agents? Are hypotensive agents contraindicated? I might point up this question a little better. These accidents often occur in people with hypertension. Statistically, it even appears that those with hypertension have a higher incidence of thrombosis than hemorrhage. Although there is some swing toward hemorrhage as the blood pressure is elevated they still have more thrombosis. Given a person with hypertension and a cerebral accident: are you going to treat his hypertension and attempt to lower his blood pressure or are you going to keep it up and why?*

DR. FAZEKAS: I think it is generally agreed that it would be desirable to reduce the diastolic pressure in the patients who have hypertension and overt evidence of cerebral vascular disease. The rate of flow through the brain is determined by the mean arterial pressure and the vascular resistance. With cerebral vascular disease there is an increase in cerebral vascular resistance and reduction in rate of cerebral blood flow. We feel that if one is to reduce pressure in patients with hypertensive cerebral vascular disease, it should never be reduced to normal values because of the increased cerebral vascular resistance. We have noted that the mean arterial pressure at which patients develop signs of cerebral ischemia may vary considerably from patient to patient. For example, a normotensive subject can withstand a mean arterial pressure as low as 30 to 40 mm. of mercury without developing signs of cerebral ischemia. The patient with hypertensive cerebral vascular disease or malignant hypertension may develop signs of ischemia at normotensive levels. Since most hypotensive agents in use today may cause precipitous reductions in pressure even on changing position, the dose should be

regulated so that the blood pressure is never allowed to drop to normotensive levels but is maintained at somewhat higher values.

MODERATOR WRIGHT: *Are there any other comments? We have received quite a few questions dealing with anticoagulants. Perhaps because our laboratory is largely responsible for raising the question, I should open this discussion and then ask for comments and criticisms.*

We must divide the problem into several sections. If there is any evidence of hemorrhage—and here spinal tap is extremely valuable, although it is not 100 per cent proof since bleeding can be into the brain tissue—if there is any evidence in terms of bleeding or frankly xanthochromic fluid, anticoagulants are contraindicated. That leaves us with the individuals with thrombosis or embolism and there are a large number of these. The use of anticoagulants is a new approach. It must still be regarded as exploratory but thus far we have information which suggests the following: that it is necessary to divide patients into those who have had acute recent brain lesions, and those who have had one or more lesions in the more or less distant past. The question of the use of anticoagulants for the acute episode is still a moot point. We are in the process of examining this. Dr. Ellen McDevitt and our team at Bellevue and New York Hospitals are working continuously trying to get a control series together and a committee has been set up on a national basis, to try to determine whether or not it is wise to use anticoagulants for the treatment of an acute attack.

One of the reasons for hesitancy is that around infarcts, wherever they occur in the body, whether it be the heart, kidney or the brain, there is hemorrhage into the surrounding tissue. Careful studies by Herrman Blumgart and by others, and by the Committee on Anticoagulants of the American Heart Association, suggest that this does not influence the outcome of a myocardial infarction, in terms of anticoagulant therapy. The hemorrhage is not greater, does not last longer,—it did not in dogs and does not seem to in man. The same may be said about renal infarcts but in these tissues the damage is not necessarily so irreparable. Brain tissue has a poor comeback. Perhaps Dr. Adams will correct me in that regard but it is my impression that brain tissue is damaged more easily and more permanently in terms of function than other types of tissue. Our position for the present is that we are interested in and are studying this problem but we have no definite conclusions regarding the use of anticoagulants in the treatment of

acute episodes. Individuals who have repeated mild episodes, which may be due to spasm or tiny thrombi, may receive anticoagulants in an attempt to head off more serious lesions. Unfortunately, we cannot tell whether they are going to develop a more serious episode or not.

There is a second group of patients which we have been studying. This group consists of individuals who have had one or more cerebral episodes in the past. We have followed them without anticoagulant therapy and then for comparable periods of time on anticoagulant therapy to see what their history in terms of thrombo-embolic episodes would be. I would like to read just a few figures. Most of them have been published and are available. In order to establish valid controls we have used the patients themselves as their own controls. For example, a group of 19 patients with generalized arteriosclerosis and with cerebral lesions were studied for 246 patient months, during which time they developed 48 thrombo-embolic episodes of which 25 were cerebral. They were then established on a regimen of anticoagulants, and studied for a little longer time, 287 months, during which interval, instead of 48 total thrombo-embolic episodes, there were only eight, and instead of 25 cerebral episodes there occurred only two. Fifty-seven individuals who started as cerebrovascular cases were studied for approximately 800 months during which time they had 205 thrombo-embolic episodes, of which 81 were additional cerebrovascular episodes. The same 57 patients, who after the control period were that much older, were then studied for a third longer time, 1100 months, during which time instead of 205 episodes they suffered only 23, and instead of 81 cerebral episodes they had six. We studied a group of 31 rheumatic heart disease patients with fibrillation and emboli. They were studied for 463 patient months, during which time they had 137 thrombo-embolic episodes of which 46 were cerebral. The same patients were then studied for nearly twice as long, nearly 700 months, during which time instead of 137 total thrombo-embolic episodes there were 11. Instead of 46 cerebral there were four. A total of 85 patients who had previously suffered one or more cerebral vascular episodes and who were followed 3600 months with no anticoagulant therapy, developed 290 total thrombo-embolic episodes and 154 cerebral episodes. The same 85 patients, that much older, studied for an equivalent length of time while on anticoagulants, developed only 32 thrombo-embolic episodes of which 12 instead of 154 were cerebral episodes. This suggests that even though the use of

anticoagulants for the acute episode may be debatable at this time there is rather strong evidence that these patients who normally tend to have repeated thrombo-embolic episodes—as demonstrated by the above figures—do receive a very definite degree of protection by the use of long term anticoagulant therapy.

That sums up the present status of our work. I am glad to give credit for much of this work to Dr. Ellen McDevitt, Dr. William Foley and others who work on this project.

DR. MERRITT: I would like to ask Dr. Wright if he believes that the administration of anticoagulants has any effect on the existing lesion.

MODERATOR WRIGHT: In the past it has been generally held that a thrombus or an embolus once formed was not affected by anticoagulant therapy in terms of dissolution of that particular clot. However, there is now very good evidence produced by Dr. Helen Paling Wright (no relative of mine) of London, and by others, that this is not the case but that clots or emboli especially in their early stages when they are fairly soft can, by the use of anticoagulants, be exposed to what are presumably enzyme systems of the blood which do in fact hurry their dissolution. So that we are not only preventing propagation of the original clot or the development of additional thrombi elsewhere in the system but may actually be having a definite effect on the original clot.

DR. MERRITT: You do not believe that the removal of clot can have any effect on the brain tissue that has already been damaged?

MODERATOR WRIGHT: We do not have evidence of this. With myocardium and renal tissue, we still can obtain a marked return of function after damage. But with brain tissue the restitution is less complete.

DR. MERRITT: I would like to ask Dr. Wright another question. When you once start giving anticoagulants does the treatment have to be continued for the remainder of the life of that patient or do some patients go through critical episodes that can be controlled by anticoagulants and then the medication withdrawn after a period of weeks or months?

MODERATOR WRIGHT: This is a major problem. Originally we felt it was safer to study this problem in patients with thrombophlebitis than in patients with more serious types of lesions. There are individuals who have been placed on long term anticoagulant therapy after having had as many as a dozen attacks of thrombophlebitis. Later, attempts have

been made to discontinue anticoagulant therapy,—often with prompt recurrence of their thrombophlebitis. They apparently have some fundamental change in their clotting mechanism which our and other laboratories have failed to clarify. Nevertheless, it is there. Some of these patients can never remain off anticoagulant therapy without returning to the same condition and having new clots appear within a period of months and in about the same numbers as before they were given anticoagulant therapy. We usually discuss this problem with the patients at the end of a year, explaining the risk and also giving them the choice of trying to get along without anticoagulants. Some do not suffer a relapse but many do. When we take them off anticoagulants there is some risk of another episode. If a patient wishes to take that risk as against the inconvenience and expense of therapy, he should be watched closely. If they develop the same type of thrombosing episodes, then as far as I am concerned, they are on the regime for life, because we have no other solution.

DR. ADAMS: One criticism that might be offered in connection with your data is that the control period in each instance preceded the treatment period and if there is any possibility that these thrombo-embolic phenomena tended to run a clustering course, many episodes in the first year or two and then less frequent ones thereafter, that would partly explain your good results. Perhaps you have some data which would compare the treatment period with the subsequent control period without drugs.

MODERATOR WRIGHT: We have two types of answers for that question. In the first place we have many individuals who have had embolic and thrombotic episodes over a period of years prior to the use of anticoagulant therapy. One woman had 21 episodes, of which 9 occurred in the ten days preceding her being placed on anticoagulants in 1946. She was kept on heparin for a brief time, then dicumarol from 1946 to 1950. She had no episodes. In 1950 she revolted against the regimen and went a month without anticoagulants. At the end of a month she had a large saddle embolus. She went back on anticoagulants and she has been on anticoagulants ever since, five years, without another episode. Now considering she had 21 episodes over a period of some five or six years prior to treatment, some of them very serious, it appears as though we have strong evidence of a therapeutic effect. The other group includes those reported in the article which has recently appeared from

our laboratory. We have compared the courses of individuals who have been intermittent in their therapy as compared with those who have been faithful and continuous in their therapy, in periods up to eight years. The outlook for those who have been intermittent in their therapy has been infinitely worse, with many more complications. These are people who would stop therapy and after some months develop an episode or two. They then went back on therapy again. Their episodes would cease, they would stop treatment with more trouble, etc. We have comparative tables of those who have been on intermittent therapy. In those cases, the control or untreated periods have not always preceded the therapy. These have been published and they are available for study.

DR. FAZEKAS: Have you treated a sufficiently large group of patients who have hypertension and cerebral thrombosis and do you give both anticoagulants and hypotensive agents to these people?

MODERATOR WRIGHT: This is really a knotty problem. I personally much prefer that they do not have hypertension and many people with cerebrovascular disease do not have it. The point we have not quite decided upon is the blood pressure level above which we should not give anticoagulants. At the Mayo Clinic they are more courageous than we are. We have patients on anticoagulants who have carried pressures of 230/130 but I prefer not to have that. The only reason we put such patients on the regimen is that they have repeated thrombotic episodes and it appears as though they are headed for an early demise. Some of them have done remarkably well. One woman over 80 carries a pressure of more than 200/110 and has been on anticoagulants six or seven years and done extremely well. But there is this calculated risk. I don't think anybody ought to have any illusions about it. The patient's family, the doctor, all must understand. It is like major surgery for a carcinomatous lesion. There is a risk. The patient may not survive the treatment. You have to weigh it and decide which seems to be the wisest course.

Dr. Merritt, I would like to ask you what you are doing in the way of anticoagulant therapy.

DR. MERRITT: Unfortunately we are not conducting a controlled study of this form of therapy, but we are giving anticoagulants to patients with lesions that are thought to be thrombotic or embolic in nature, excluding the hemorrhagic phenomena, but we still do not know how long to continue the therapy.

MODERATOR WRIGHT: *I think we will now discuss another type of*

therapy which has recently been advocated. This concerns the use of cortisone for the acute cerebral episode. Dr. Fazekas, what do you think about the use of cortisone for the acute episode, can you evaluate the work upon which this claim is based?

DR. FAZEKAS: I also read the article in J.A.M.A. in which cortisone was recommended for the management of these patients. I don't think that I would agree with the author that cortisone should be given routinely to such patients. I am greatly impressed with the side effects of cortisone. With respect to edema, I should think because of cortisone's sodium retaining properties, it probably would, if anything, enhance edema formation.

MODERATOR WRIGHT: *Dr. Merritt will you comment on this?*

DR. MERRITT: I would agree with those remarks. I see no physiological reason for giving cortisone.

MODERATOR WRIGHT: *Dr. Adams!*

DR. ADAMS: No.

MODERATOR WRIGHT: *Dr. Covalt!*

DR. COVALT: We have not used it at the Institute.

MODERATOR WRIGHT: *There is another aspect of cortisone which was not covered in the recent article. This has to do with the question of the value of cortisone or steroids in the chronic cases and I think Dr. Covalt's group has had some experience in this area. This is after the acute phase has passed,—when the patient presents certain problems in relation to his long-term management.*

DR. COVALT: We have not used cortisone in the acute case. We do not see the acute case at the Institute. We have used the steroids occasionally in the patient who does not do well in the rehabilitation program,—this may be some four, eight or twelve weeks past the acute onset—who is not eating well, is not interested, and seems to lack motivation. There is no apparent reason why he should not go ahead with his treatment,—he cerebrates; he is oriented as to time and place. Sometimes by using very small doses of cortisone we have seen these people start on the rehabilitation program, begin to eat and actually to make the difference between success and failure, as far as this patient becoming self-sufficient is concerned. Again, this group includes a small selected number of cases. We feel it has been helpful in certain cases but I cannot report sufficient numbers to warrant saying that it is definite.

MODERATOR WRIGHT: *Dr. Covalt, we have discussed pathology,*

anatomy and physiology, some types of therapy and now we have come to the patient who, having survived his attack, needs help and we turn to the rehabilitation group. We now turn to you for help.

DR. COVALT: That is quite an order because these patients must survive before I get to see them.

MODERATOR WRIGHT: *How soon should a patient with hemiplegia following a cerebrovascular accident be started on rehabilitation?*

DR. COVALT: We who are in rehabilitation must depend upon you internists and neurologists to tell us from the clinical standpoint how soon we can start rehabilitation. In surveying our records over the past several years, we find that there have been no untoward effects in those patients with hemiplegia, due either to thrombosis or embolism, in starting rehabilitative measures within the first 48 to 72 hours. First, the positioning of the patient at the time of the acute onset is very important in order to prevent the contractures we see so often with these patients. Outward rotation of the paralyzed leg should be prevented by means of sand bags and it is important to keep the foot at a right angle to the leg to prevent heel cord shortening. The outward rotation can be prevented by means of sand bags placed laterally along the side of the leg and a foot board may be used to prevent foot drop. Better than either of these, if available, is a little posterior splint made with "dog ears" so that the foot is kept at a right angle and the "dog ears" on the posterior splint will prevent outward rotation.

The position of the arm is important and by using many small pillows, the arm should be kept away from the chest with the elbow higher than the shoulder, the wrist higher than the elbow, and the fingers and hand higher than the wrist. This helps to prevent the edema that is so common in these patients.

A physical therapist, nurse, or even a member of the family should be instructed to take the paralyzed extremity through a complete range of motion of all the joints twice daily. This can be done with little or no disturbance to the patient. This would be a passive exercise.

As soon as the clinician feels that the patient can be put on a more active program, then strengthening exercises should be given for the weakened muscles of the paralyzed side.

As soon as the clinician will permit, the patient should be allowed to sit up in bed—at first, with help and later, he should be encouraged to do so by himself. The patient should be allowed to sit on the edge

of the bed with his feet on the floor as soon as possible because in the older-age group, these patients quickly lose their sense of balance and it may take days and weeks of work in order for them to get their sitting and standing balance again.

It is important that these people not only be allowed but encouraged to stand as soon as possible. In the home, I often bring two ordinary ladder-back chairs to the bedside and allow the patient to stand between the backs with his hands resting on both backs, and, with assistance, try shifting his weight from one side to the other in order that he may preserve standing balance. Within the next few days, an ambulation program should be started preferably between parallel bars or with crutches—and even a cane may be used.

MODERATOR WRIGHT: *Dr. Covalt, we know the prognosis is rather poor for a completely paralyzed upper extremity. Is it sufficiently poor to prevent a patient from going ahead with the rehabilitation program? Do you think his disability ought to be accepted or he be put through the expense and the effort of the rehabilitation program?*

DR. COVALT: The completely flail extremity presents a problem and many of us know the prognosis is poor, if there is no muscle action of any kind. I still think the arm should be supported carefully with a little sling so the patient does not get subluxation that becomes painful to these patients. Careful attention must be given to see whether there are any muscular contractions of the extremity. I would not spend a lot of time in physical therapy on the arm if there are no muscle movements. However, the point to the question is this, it still does not mean that this man is going to have to stay in bed or is going to have to have somebody to nurse him around the clock. This man can be taught to be self-sufficient, to dress himself. We teach men to tie their shoe strings with their other hand,—to put on neckties with one hand. We have men working, driving their own cars with a completely flail upper extremity. A man can be completely rehabilitated with one completely flail upper extremity.

MODERATOR WRIGHT: *There is one other question I would like to ask you. It has to do with painful shoulder. We have been talking about cerebral vascular diseases but following myocardial infarction and seemingly almost unrelated, patients develop painful shoulders. Have you some comments? How can this be prevented? What is your best technique?*

DR. COVALT: Pain in the upper extremity is one of our big problems. I have not found any medication that helps. One thing that can be helped however is the painful arm following hemiplegia that has become ankylosed and stiff. You may assure such a patient that if he will go through the routine of getting this arm into complete extension once more, whether by active or passive means, he will not have pain in that arm again. Sometimes a member of the family can gently stretch this arm. As soon as he gets the arm to complete extension again, he will be rid of his pain in that arm. That is for the ankylosed or fibrosed shoulder joint. The other pain that baffles us and which we find most difficult to control is an intractable lightening-like pain. I am sure it must be central in origin and I have not found anything which satisfactorily relieves it.

MODERATOR WRIGHT: *Dr. Adams, do you know how to treat it?*

DR. ADAMS: All we do is wait for six, eight, twelve months, for it to go away.

MODERATOR WRIGHT: *Does it?*

DR. ADAMS: Yes. Sometimes the doctor, the family and the patient have contemplated surgery on the brain for the patient who is suffering from so-called thalamic pain. If one waits just a few more months it may subside.

DR. COVALT: I have one patient waiting for three years.

DR. ADAMS: That may also happen of course.

MODERATOR WRIGHT: *Dr. Merritt, what do you do?*

DR. MERRITT: I do not know of any effective treatment for so-called thalamic pain, but I think Dr. Covalt ought to point out that pain in the shoulder that follows fixation of the joint is often the result of poor treatment in the initial stages.

DR. COVALT: Very true.

DR. MERRITT: This is something that we ought to avoid, and the treatment of these patients can be started immediately when you put them in bed. As pointed out if their extremities are placed in the proper position you will not get these contractures. Also by beginning passive movement almost as soon as the patient is able, you prevent contractures.

MODERATOR WRIGHT: *Dr. Fazekas!*

DR. FAZEKAS: We don't have any special treatment for this type of pain. We have been using the tranquilizing drugs, and some patients

seem to be detached from pain and somewhat less agitated following their administration. I would like Dr. Covalt to talk a little more about the selection of patients for rehabilitation. Rehabilitation, as I understand it, is a fairly expensive undertaking that involves not only physical therapy but occupational therapy and vocational training. Is there any way we can select patients and predict what patients may be considered as good risks for such an expensive undertaking?

DR. COVALT: It is a very good question. I must point out that one must be as ruthless in selecting patients for rehabilitation as in selecting therapy for patients with cancer,—whether to use x-ray, radium, surgery or to do nothing. Rehabilitation is no miracle. It is a program of very simple things—and hard work.

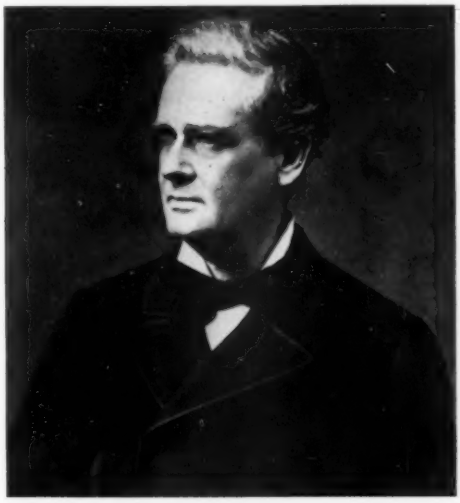
I found that the longer that I am in this particular branch of medicine the more I continue to be amazed at what the patient can do. However, there are some patients who are not suitable for rehabilitation. This group would include those patients with malignant hypertension, with advanced senility and those patients with advanced encephalomalacia. A good rule to remember is that the patient who cannot remember tomorrow what is taught to him today is not a good candidate for rehabilitation. Many patients with hypertension are suitable for rehabilitation; in fact, we find that during the course of a rehabilitation program, that many of these pressures are reduced. Every patient with hypertension must be given a graded exercise program. Short periods of modest exercises are given with prolonged rest periods.

We must also remember that we see many patients who have edema for the first several weeks after onset who gradually clear mentally and who respond well to an active rehabilitation program at that time.

If a patient is not considered suitable for rehabilitation, the patient, of course, is not told, but the family must be so advised. The patient is sent home with a modest exercise program to be carried out by the nurse, family or physical therapist. If he improves over a period of weeks, he may become eligible for an active rehabilitation program.

Actually, in our experience at the Institute of Physical Medicine and Rehabilitation, we have found the percentage of patients who could not be helped quite low.

MODERATOR WRIGHT: I want to thank the members of the panel and the audience for their participation. We must now conclude this Conference on Cerebral Vascular Diseases.



J. Marion Sims, 1813 - 1883
Photograph from the collection of Arthur Reich, M.D.

THE INFLUENCE OF J. MARION SIMS ON GYNECOLOGY*

Claude E. Heaton

Gynecology as a surgical specialty may be said to have had its beginnings when in 1809 Ephraim McDowell performed the first successful ovariotomy and when in 1849 J. Marion Sims opened up the field of vaginal plastic surgery with his work on vesico-vaginal fistula. It is the purpose of this paper to describe briefly Sims' pioneer achievements in surgery and to trace his influence on gynecology down to the present day. The temptation is great to stray from my assigned topic into the byways of biography for the story of Sims' life is a fascinating one. But it is a tale often told, by Sims in his autobiography, and by many others. Especially noteworthy is the delightful monograph by James Pratt Marr which appeared in 1949.

Gynecology was in a sad state in the first half of the Nineteenth

* Presented at a combined meeting of the Section on Historical and Cultural Medicine with the Section on Obstetrics and Gynecology at The New York Academy of Medicine, March 14, 1956.

Century with the "pessary school" in the ascendency. It was said that two fortunes were easily made in gynecology—one by those who inserted pessaries, and the other by those who removed them. The term gynecology was not used until 1847. The family doctor who treated diseases of women was "doing nothing with a deal of skill." Women were exceedingly modest with the result that an adequate examination was seldom made and there was little understanding of the nature of diseases of the reproductive organs. In 1854, Charles D. Meigs, Professor of Obstetrics and Diseases of Women and Children at the Jefferson Medical College, had "urged as a valid objection to gynecological examinations the likelihood of inducing a lax moral sense in the patient."

Sims states in his autobiography that if there was anything he hated it was investigating the organs of the female pelvis. During his first ten years of practice he never pretended to treat any of the diseases of women, referring them elsewhere.

Sims' first achievement was the cure of vesico-vaginal fistula. His accidental discovery of the value of the knee-elbow position in obtaining the necessary exposure for a surgical attack on the lesion and his invention of the vaginal speculum which bears his name, were the first steps taken on the road to success. Beginning in 1845, Sims spent four years attempting to close a fistula, operating on three patients some 40 times. Finally, he hit upon the use of silver wire as suture material. Success came in June, 1849, when Sims finally cured a patient he had operated on 30 times. His classic paper *On the Treatment of Vesico-Vaginal Fistula* was published in *The American Journal of the Medical Sciences* in 1852. The author described what he believed he had originated: the position of the patient for the operation, the speculum, the means of vivifying the edges of the fistulous opening, the suture apparatus, and the catheter. He reviewed the work of others, notably Jobert of France and in this country, Hayward, Pancoast and Mettauer. All had succeeded in curing a few cases of vesico-vaginal fistula and Mettauer had used lead sutures.

Actually none of Sims' innovations were exactly new. As Marr points out, his great achievement was "that of perfecting and popularizing a technique which was simple in principle and more nearly universally applicable than any technique previously devised."

The Sims operation for vesico-vaginal fistula is by no means outdated. According to J. Chassar Moir of Oxford, as late as 1916 Herbert

Spencer, the foremost exponent of Sims' method in Great Britain, repeatedly succeeded in effecting a cure by the simple procedure of paring the edges of the fistula and drawing them together with silver wire. He succeeded even in patients who had been subjected to previous operations by other methods. Moir in 1940 stated that he always used Sims' semi-prone position and silver wire.

In *The American Journal of Obstetrics and Gynecology* for March, 1956, there is a valuable article by J. C. Moir entitled *Personal Experiences in the Treatment of Vesico-Vaginal Fistula.* He writes that it was the challenge of vesico-vaginal fistula that, in large measure established gynecology as a specialty and provided the stimulus for the creation of the earliest gynecological hospitals.

Moir states that at one time, in accordance with the Marion Sims tradition, he employed silver wire and was well pleased with the results. In his opinion the most serviceable retractor is a medium or small-sized Sims speculum. It is interesting that at this late date Moir finds it necessary in his conclusions to caution: "don't despair of local closure of a vesico-vaginal fistula."

The only advance made since the introduction of Sims' techniques has been the separation of the bladder from the vaginal mucosa and the suturing of each as an individual layer. The flap-splitting operation was devised by Colles of Dublin in 1857 and developed by Mackenrodt in 1894.

The second great achievement of J. Marion Sims was the founding of the Woman's Hospital in the State of New York in 1855. This unique institution, the first hospital in the world for the treatment of the diseases of women, was the second great influence which Sims exerted in the development of the specialty. Here over the past century many of the leaders received their training and advanced gynecology by numerous contributions.

During the Civil War, Sims spent six years abroad where he was warmly received by the leading members of the profession. One result of Sims' voluntary exile was the opportunity it gave him to find the time to produce his one book on the subject of gynecology, *Clinical Notes on Uterine Surgery; with Special Reference to the Management of the Sterile Condition.* First appearing serially in the *Lancet* in 1864 and 1865, it was published in book form in 1866. Editions of the book were printed simultaneously in London, New York, Paris, and Erlangen,

Germany. Sims did not claim to have written a systematic work, nevertheless it established his reputation as the leading gynecologist in the world and was another great step forward in making gynecology a surgical specialty.

Sims was severely criticized for his frankness about the treatment of sterility. He was many years ahead of his contemporaries in advocating the use of the microscope as an aid in the diagnosis and treatment of sterility. He outraged his Victorian readers by his description of post-coital examination of the sperm and his use of artificial insemination. *The Medical Times and Gazette* of London expressed "an unfeigned regret that Dr. Marion Sims had thought proper to found an odious style of practice on such methods. Better let ancient families become extinct than keep up the succession by such means."

In numerous papers, Sims advanced the growth of the specialty. He contributed to the surgery of prolapse of the uterus, advocated hysterectomy for bleeding fibroids, urged the "extirpation of the cancerous uterus" as the only means of curing uterine malignancy. Deeply interested in the whole problem of cancer, he urged the establishment of a hospital for the exclusive treatment of the condition. His plea was largely influential in founding the New York Cancer Hospital, now the Memorial Hospital.

But Sims did not confine himself to pelvic surgery alone; he was a pioneer in the surgery of the abdomen along with Lawson Tait and Joseph Price. At the age of 68, Sims made his last great contribution. It was based on his experiences at the battle of Sedan in 1870 while serving as chief surgeon of the Anglo-American Ambulance Corps. The mortality from gunshot wounds of the abdomen was 100 per cent at that time. In what proved to be his valedictory address, delivered before The New York Academy of Medicine on October 6, 1881, he pleaded for the immediate exploration of the abdomen in suspected perforation of the bowel, hemorrhage from ectopic pregnancy and other intra-abdominal accidents. In the discussion which followed, his views were considered too radical. Yet in little more than a decade Sims' forecast of the surgery of the future was widely accepted.

J. Marion Sims died at the age of 70 on November 13, 1883. The founder of gynecology left a name, which in the words of the poet, was:

"One of the few, the immortal names,
That were not born to die."

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting of October 27, 1955, at The New York Academy of Medicine

Pathologic Aspects of Lung Expansion in Mature and Premature Newborn Infants

PETER GRUENWALD

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This presentation is concerned with those factors affecting aeration of the lungs which reside within the pulmonary parenchyma and operate in the presence of an intact neuromuscular respiratory mechanism and with patent respiratory passages. They include surface properties of the respiratory spaces and anatomic peculiarities which exist particularly in premature infants.

Surface properties include the manifestations of surface tension and a peculiar form of adhesiveness of alveolar walls. Surface tension tends to reduce the surface area between gas and liquid (or moist tissue) to a minimum,—that is, it makes air form the fewest and largest possible bubbles. Whenever air is introduced into an airless lung, this force must be overcome; in experimental expansion of lung specimens this is shown by higher pressures required to introduce air as compared with water or similar liquids. Other experiments, as yet incomplete, suggest that surface active agents (detergents) may be useful in overcoming surface tension. Another property of respiratory surfaces in the lungs was recently demonstrated by James.[1] If newborn animals breathe for a short period of time and their lungs are then made to collapse, these lungs offer a greater resistance to expansion than do those of litter mates killed before the onset of respiration. A peculiar adhesiveness of surface counteracts re-expansion.

Two anatomic features affecting pulmonary aeration in premature infants are based on incomplete development of the alveoli proper. One of these tends to prevent the progress of aeration from the bronchioles to the alveoli; the other one favors the collapse of previously aerated lung parenchyma.

In premature infants the bronchioles are relatively large and easily distended with air, whereas the alveoli are still small and air enters them with difficulty or not at all, owing apparently to the tendency of air to form large bubbles. At term the alveoli have grown and the disparity in the size of alveoli and bronchioles diminishes accordingly. Air will now expand bronchioles and alveoli alike. Actually the lungs of premature infants obtained at autopsy often show expanded and even distended respiratory bronchioles while the alveoli are collapsed; this is the characteristic *atelectasis of prematures*. It can be artificially produced by introducing air into lung specimens obtained at autopsy from premature infants. If one lung is treated in this way, and the other lung of the same infant is inflated simultaneously with fluid under the same height and duration of pressure, the latter will show uniform expansion of alveoli without excessive distention of the bronchial tree. It thus appears that a structural pe-

culiarity, equally present in the excised lung and in that of the living infant, favors development of atelectasis of premature infants.

The second structural characteristic produced by incompletely developed alveoli is expressed by the ratio of capacity of the alveoli and the bronchial tree. Compared with the mature infant, this ratio is shifted in favor of the bronchi when premature infants are considered. If, for example, at a certain stage the ratio is 1:1, then removal of half the amount of air from a lung results in complete loss of air from the alveoli and atelectasis. This has been demonstrated in lung specimens from premature infants. It is quite possible, during periods of apnea which are known to occur in many newborn infants, that a considerable amount of air leaves the lungs either by expiration or by absorption of oxygen in the lungs, if a high oxygen mixture has been administered. In premature infants atelectasis may rapidly develop and need to be overcome when respiration is resumed.

It is therefore suggested that three factors contribute to the development of the pattern of atelectasis of premature infants, which is characterized by distension of respiratory bronchioles and collapse of alveoli: 1) a low ratio of capacity of alveoli vs. bronchi in premature infants favors the loss of air from the alveoli when only part of the total volume of air leaves the lungs; 2) in conditions of collapse following air breathing the respiratory surfaces have an increased adhesiveness, tending to perpetuate atelectasis caused by the first factor; 3) when lungs are only partially aerated, surface tension favors the formation of large air bubbles in the bronchioles, rather than smaller ones in the alveoli.

Hyaline membranes do not occur in all instances of atelectasis of premature infants, but only in those in which air in the respiratory bronchioles is replaced by fluid. These membranes are therefore not the cause of atelectasis. They probably consist of inspissated edema fluid after most of its water has been absorbed.

REFERENCE

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DISCUSSION

WILLIAM A. SILVERMAN: I should like first to pay tribute to Dr. Gruenwald's lucid presentation and to acknowledge the debt that we owe to Dr. Gruenwald, Dr. James and Dr. Wilson for pointing out how naive many of our concepts have been up to this point. As clinicians we have been looking for the perfect mechanical device that would somehow puff out the lungs of the premature infant. As has been pointed out tonight, the physical problem presented by the collapsed lung of the newly born premature infant is truly a formidable one. Clinically we are more often presented with the problem of the re-collapsed lung or, as it has been called, the "Swiss cheese" type of atelectasis from its microscopic appearance. As Dr. Gruenwald and Dr. James have now pointed out, these lungs may be very different from the initially atelectatic lung. Certainly current methods of dealing with these secondarily atelectatic lungs have not resulted in any striking improvement. I believe I have been chosen to come here tonight to debunk mists or more specifically detergent mists. I don't particularly enjoy this role because it may well be that the detergents, when used differently, will be of some help in solving this problem. However, I must report that both detergent and water mists when used as prophylaxis have failed to influence the rates of dying of premature infants in our nursery. We undertook a controlled study of these mists in the premature nursery of Babies Hospital about two years ago. Upon admission to the nursery, infants were entered into the study and assigned in random order to either mist therapy or 90 to 100 per cent relative humidity. Two such studies were carried out, one testing Alevaire mist vs. 90 to 100 per cent relative humidity, the other water mist vs. 90 to 100 per cent relative humidity. Each study involved 200 infants and took ten months to complete. The mortality rate in the Alevaire mist group was not significantly different from the rate in the control group. The pulmonary findings (hyaline membrane, atelectasis, pneumonia, etc.) were not significantly different in the two groups. The same was true when we compared water mist with 90 to 100 per

cent relative humidity. In addition, the clinical course of the premature infants was no different in the water mist and control groups.

I am much interested in Dr. Gruenwald's paper and I would like to say that his suggestion of using a surface-acting agent should not be discarded simply because of our negative results with a detergent mist. Perhaps an extrapulmonary aerator could carry these infants along until one could pour down a liquid preparation into the lungs of these infants and bring about re-expansion as neatly as we have been shown here tonight.

CHARLES F. BEGG: I should like to ask Dr. Gruenwald if he can really compare the type, character, and degree of expansion obtained by injecting material into the bronchi under positive pressure with the sort of expansion obtained by expanding these lungs under negative pressure, which is more physiological.

PETER GRUENWALD: That question is frequently asked. As far as I know there is no difference. Suppose you were on the top of Mt. Evans. You might be able to expand a lung by applying to a bronchus 760 mm. pressure. By local standards you have used positive pressure on the bronchus, but by sea level standards you have applied negative pressure on the outside. However, there is another factor which may be significant, and that is the difference between a lung in the chest and a lung in a jar. There, I think, caution is more advisable. I have only gone into the very basic factors concerning the alveoli and bronchioles, but I am quite certain that the lung as a whole behaves differently when it is in the chest than when it is expanded in a jar.

LOTTE STRAUSS: It would seem that the main respiratory problem in these premature infants is connected with secondary atelectasis, very frequently due to apnea. Air which has been present in the previously expanded alveoli is absorbed and consequently the collapsed portions of the lung will suffer from oxygen lack. Apparently there are circulatory changes associated with anoxia, and vascular damage, which cannot be reproduced in the excised lung. Most of the premature lungs in which we find "hyaline membranes" contain fluid, the accumulation of which should perhaps be attributed to local tissue anoxia within the lung.

I should like to ask Dr. Gruenwald if he thinks the "stickiness" may be due to the accumulation of fluid, perhaps edema fluid, in the lung. I do not know whether a situation comparable to that in the living infant can be reproduced in an experimental model with an excised lung deprived of its circulation, i.e., with purely physical means.

Dr. Gruenwald's demonstration of how easily the premature lung loses its alveolar air points to an important clinical problem, namely the prevention of secondary atelectasis. Is it possible to create conditions whereby the absorption of gas from the alveoli can be slowed sufficiently to tide the baby over his apneic spells without atelectasis ensuing?

PETER GRUENWALD: I will agree that in anoxia edema fluid is more likely to pour out into the air spaces and may very well have something to do with increased adhesiveness. The prevention of collapse of the lung cannot be accomplished by any amount of oxygen which one may administer to the lungs; as I mentioned previously, nitrogen will keep the lungs open. This is just another reason for not giving too much oxygen. Perhaps conditions will be a little better now since, out of respect for retrolental fibroplasia, one does not give as much oxygen as previously. It might be interesting to study any differences in the lungs of premature infants from the time when much oxygen was given and from more recent times, when little oxygen is used. However, these infants are in respiratory distress, and I do not think any of them die without being given extra oxygen.

H. P. SMITH: Is the detergent supposed to eliminate stickiness?

PETER GRUENWALD: Originally the detergent was used to lower surface tension. To what extent we can combat stickiness is another problem. People have maintained that mucus can be dissolved by detergents. This, as Dr. Silverman points out, is a wide-open field, and the failure of the effect of one preparation used as prescribed on the package, does not prove that detergents will

be ineffective under all circumstances.

H. P. SMITH: Have any test tube studies been made to show whether detergents or other agents, would destroy the stickiness of mucus or of other like materials which might be present in the lungs?

PETER GRUENWALD: As far as I know, they have not. This work of James is quite recent. We worked at Kings County Hospital last summer, and I have not seen him since. But as far as I know, he has not come up with anything new.

Nuclear Myelopathies of Childhood

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Nuclear myelopathy is used to designate those pediatric illnesses, progressive or otherwise, resulting from diffuse destruction of the anterior horn cells of the spinal cord. Focal spinal lesions, secondary to trauma or anomalous development, would not be considered in this category. With the exception of cases attributable to infection such as poliomyelitis, little is known about the causation of such diseases. There are three clinically defined entities which can qualify as instances of nuclear myelopathy. The first is amyotonia congenita; the second, infantile progressive muscular atrophy, and the third, arthrogryposis multiplex congenita.

The summarized findings are based upon observations in two cases of amyotonia congenita, one case of infantile progressive muscular atrophy, and three cases of arthrogryposis. In all instances muscle biopsies were performed, often serially, and in five instances, necropsy data are available.

The one point of clinical junction between the three entities is a significant degree of neuromuscular disability. In amyotonia and arthrogryposis the paresis is obvious at birth. In infantile progressive muscular atrophy, the derangement does not become overt until the sixth to tenth month of life. Prognosis in amyotonia and arthrogryposis is relatively favorable, in contrast to the poor outcome in most cases of infantile progressive muscular atrophy, where a continuing clinical deterioration has been repeatedly described. No familial tendency is apparent in arthrogryposis, while this is characteristic of the other two diseases. Also in contrast to the universal flaccidity of amyotonia, a joint rigidity with some spasticity is prominent in arthrogryposis. Finally, in cases of arthrogryposis there are numerous other developmental anomalies involving non-neural somatic tissues.

Clinically the three diseases can be differentiated with ease. The pathologic lesions within the central nervous system and skeletal musculature of all three, however, tend to be indistinguishable. Autopsies in cases of amyotonia congenita disclose a salient diminution in the number of spinal cord anterior horn cells, the residua showing varying stages of trophic degeneration and atrophy. Lateral and posterior horn cells are singularly uninvolved. Myelin stains show a secondary atrophy of the anterior motor roots. Within the peripheral musculature a pattern of relatively normal muscle fibers alternating with distinctly atrophic muscle cells is seen. Topographically, the limb muscles are involved to a measurably greater degree than the trunk musculature. The diaphragm is histologically normal.

The pathologic features of arthrogryposis differ but slightly. Lumbar and sacral anterior horn implication appears to be greater than in amyotonia, reflected clinically in the marked atrophy of ankle muscle so characteristic of the disease. Muscle changes in arthrogryposis are otherwise identical with those of amyotonia. In addition, there is a moderate decrease in the myelin content of the corticospinal tract.

All indications point to the primacy of the central nervous system in the causation of these clinical syndromes. The histologic

pattern of atrophy in a disease such as poliomyelitis, where there can be no question of the precedence of spinal involvement, is fundamentally similar to the alterations described in these degenerative diseases. Some have contended that primary abnormality within skeletal muscle can lead to retrograde, secondary changes within the anterior horn cell components. Nevertheless, in a disease such as progressive muscular dystrophy, preeminently a primary myopathy and a disease characterized by diffuse muscular degeneration, there is a singular absence of any anterior horn cell change, even after a prolonged clinical course.

If the degradation of the anterior horn cells is the preliminary and provoking abnormality, attention is drawn to the nature of these ganglionic changes. They may represent some form of agenesis, suggested by the presence of such lesions at birth. Some have postulated a prenatal infection similar to poliomyelitis. The lack of any inflammatory stigma would not support this hypothesis. These diseases can also be conceived of as being abiotrophic in nature. If this be the reality of the situation (i.e., full development of the anterior horn cell system and secondary regression rather than primary agenesis), some morphologic evidence of this degeneration, and corroborating histologic data that such neurons were formerly present, should be anticipated. Such evidence is found in the foci of neuronophagia demonstrable in both diseases.

The differential involvement of the anterior horn cells in the nuclear myelopathies, in contrast to the apparent immunity of the lateral and posterior horn cells, is not an exclusive attribute of the three diseases in question. In poliomyelitis there is also a selective vulnerability of these cells. In other entities, such as Tay Sachs' disease, a disparate motor neuron involvement is also seen. It is apparent that ganglion cells subserving a motor function are more susceptible to many diseases, infectious, dystrophic or abiotrophic, than other cellular units of the central nervous system and, further, that this vulnerability is something intrinsic to the motor neurons rather than the extrinsic process involving these cells.

Arthrogryposis bears a superficial histologic resemblance to the adult disease of amyotrophic lateral sclerosis, an entity characterized by demyelination of upper motor neurons and degeneration of the anterior horn cells. The pyramidal tract involvement in amyotrophic lateral sclerosis assumes the previous integrity of these tracts. In arthrogryposis, however, the pyramidal system is not fully myelinated at birth, while the disease is fully expressed at this time. The infantile disease of arthrogryposis, insofar as the pyramidal tract is concerned, probably represents a more basic process and lack of development would more accurately describe the amyelination.

Joint inflexibility is the most characteristic point in the clinical presentment of arthrogryposis. The spasticity attributable to deficit in the pyramidal tracts undoubtedly contributes to this disturbance.

Some observers have also detected measurable foreshortening of the skin surrounding involved joints, a change noted in all the presently described cases. The postmortem rigidity immediately subsides following incision of the cutaneous surfaces encompassing the joints. The decrease in skin area might be an independent anomaly similar to the cleft palate seen so often in cases of arthrogryposis. It might also be viewed as a function of anterior horn cell deficiency at an early fetal age. If periarticular cutaneous area is determined partially by early motility of fetal joints, a disability of anterior horn cells emerging at a critical and primitive point of development might obviate the need for greater skin surface.

It is suggested that the factor responsible for arthrogryposis becomes operative at an earlier stage of uterine development than in amyotonia congenita. The multiple somatic developmental errors so common in arthrogryposis, and only rarely observed in amyotonia congenita, might reflect the influence of an embryonal disorder occurring at an earlier phase of growth, and thus capable of adversely affecting a broader spectrum of still undifferentiated tissues. Axiomatically, the later the point of introduction of this noxious factor, the fewer the susceptible tissues and the more focal the morphologic and clinical expression of the disease.

There is only a modicum of resemblance, clinically, between an adult with amyotrophic lateral sclerosis, a youngster with progressive spinal atrophy, and an infant with amyotonia congenita or arthrogryposis. Underlying all these disorders, however, is a basic vulnerability of the motor components of the central nervous system, and most particularly the spinal anterior horn cells, commencing in each distinct disease at a different level of somatic development, thus accounting for the frank variation in the final clinical appearance of each of these neuromuscular syndromes.

DISCUSSION

VERA B. DOLGOPOL: Did I understand you correctly to say that foci of neuronophagia were present in arthrogryposis, but not in the other two conditions?

STANLEY M. ARONSON: No, neuronophagic nodules were evident in all three of these degenerative diseases. Because of time restrictions, we displayed this characteristic change only in arthrogryposis.

VERA B. DOLGOPOL: I thought if they were present only in arthrogryposis and not in the others it might indicate that the cells were preserved longer in that disease than in the others.

STANLEY M. ARONSON: We have no quantitative data as to the number of neuronophagic foci in the three diseases.

LOTTE STRAUSS: In the families in which cases of amyotonia congenita occurred were there instances of arthrogryposis?

STANLEY M. ARONSON: As I indicated, there are only about 30-odd cases of this disease in the entire literature, and in addition, the three cases which we reported this evening. In none of these cases reported tonight, nor in those previously reported, have we found any instances of concurrent degenerative disease. Parenthetically, a disease like amyotrophic lateral sclerosis has never been considered a familial disease in this country. In certain Southwest Pacific Islands, where an extensive study has been done on this regionally common disease, a familial incidence clearly emerges. The paucity of cases in this country may be related to the apparent lack of hereditary tendency.

PETER GRUENWALD: The mechanism postulated here for the development of these diseases illustrates an important general mechanism by which malformations develop, and which was not considered in the past, when most of our knowledge of malformations was accumulated. I am referring to the occurrence of degenerative processes during development, early or late. If one searches, for instance, in hereditary malformations of animals, one finds a number of examples. I am quite convinced that this is one of the foremost mechanisms of aberrant development: structures which up to a certain point develop normally, then regress. The mechanism leading to this regression is usually not known.

HENRY SIEGEL: Is there any question of a nutritional deficiency in this group?

STANLEY M. ARONSON: I think it would be somewhat doubtful. One rarely sees an extrinsic factor, such as nutrition, playing a significant role in a disease which has a definite hereditary quality. It might be a trigger mechanism, but I do not think it has any basic etiologic significance.

LOUIS ODESSKY: In the autopsied cases of arthrogryposis was there any difference in the degree of degeneration of the anterior horns in those who lived a short time as compared to those who survived a longer period?

STANLEY M. ARONSON: We have two complete autopsies on children with arthrogryposis; the child who lived to four and a half years showed a much greater degree of spinal involvement than the child who lived for two and a half years; this is in conformity with what we are trying to bring out, namely that there is a continuing degeneration. But it may be that the child who lived for four and a half years had a basically more severe degenerative process. If we had a hundred cases and could compare them chronologically, I think we might then come to some conclusion about this.

I. JEROME SILVERMAN: You mentioned the creatine-creatinine ratio, and said that you would say more about it later; if there is time, will you please do so?

STANLEY M. ARONSON: These children continued to show abnormal urinary creatine-creatinine ratios, again indicating that the disease is progressive in nature.

THE TWENTY-NINTH

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SELECTED SUBJECTS OF CURRENT SIGNIFICANCE

MONDAY, OCTOBER 15

Evening Lectures

General Topic: THE PLACE OF HYPOPHYSECTOMY AND ADRENALECTOMY IN THE MANAGEMENT OF NEOPLASTIC AND METABOLIC DISEASES

1. Hypophysectomy in Man
   Rolf Luft, Karolinska Institute, Stockholm, Sweden
2. The Place of Hypophysectomy and Adrenalectomy in the Complications of Diabetes
   Laurance W. Kinsell, Institute for Metabolic Research, Oakland, California
3. The Place of Adrenalectomy in the Management of Severe Hypertension
   Charles C. Wolferth, University of Pennsylvania, Philadelphia, Pa.

TUESDAY, OCTOBER 16

Afternoon Panel Meeting

The Management of Disseminated Neoplastic Diseases

Moderator: David A. Karnofsky

Memorial Center for Cancer and Allied Diseases, New York City

WEDNESDAY, OCTOBER 17

Evening Lectures

General Topic: NEW DRUG THERAPY IN PSYCHIATRY AND HYPERTENSION

1. The Nature of Drugs with Mental Actions and Their Relation to Cerebral Function
   Harry H. Pennes, Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pa.
2. New Drug Therapy in Psychiatry: Clinical Uses and Abuses in Mental Disorders
   Paul H. Hoch, Commissioner of Mental Hygiene, New York State
3. A Clinical Evaluation of Hypotensive Agents
   Irvine H. Page, Cleveland Clinic, Cleveland, Ohio

THURSDAY, OCTOBER 18

Afternoon Clinical-Pathological Conference

Hypertension

Moderator: Alfred Angrist

Albert Einstein College of Medicine, New York City

FRIDAY, OCTOBER 19

Evening Lectures

General Topic: AN EVALUATION OF PRESENT STATUS OF CARDIAC SURGERY

1. Physiological Considerations and Clinical Indications for Cardiac Surgery
   H. B. Burchell, Mayo Clinic, Rochester, Minn.
2. Surgery of Congenital Heart Disease
   Robert E. Gross, Children's Hospital, Boston, Mass.
3. Surgery of Acquired Heart Disease
   Frank Glenn, The New York Hospital-Cornell Medical Center, New York City

MONDAY, OCTOBER 22

Afternoon Panel Meeting

Surgical Management of Cardiovascular Disease

Moderator: Ludwig W. Eichna

New York University-Bellevue Medical Center, New York City

TUESDAY, OCTOBER 23

Evening Lectures

General Topic: THE ADRENAL CORTICAL STEROIDS AND THEIR ANALOGUES

1. Biosynthesis of Adrenal Cortical Hormones
   Gregory Pincus, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass.
2. The Role of the Adrenal Cortical Steroids and Their Analogues in Electrolyte and Fluid Metabolism
   Louis J. Soffer, The Mount Sinai Hospital, New York City
3. Clinical Uses and Hazards of the Adrenal Hormones and Their Analogues in the Management of Rheumatic Diseases
   Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland

WEDNESDAY, OCTOBER 24

Afternoon Clinical-Pathological Conference

An Endocrine Problem

Moderator: John G. Kidd

The New York Hospital-Cornell Medical Center, New York City

THURSDAY, OCTOBER 25

Evening Lectures

General Topic: POLIOMYELITIS

1. The Nature of Viruses
   Mark H. Adams, New York University-Bellevue Medical Center, New York City
2. Present Status of Attenuated Live Virus Poliomyelitis Vaccine
   Albert B. Sabin, The Children's Hospital Research Foundation, Cincinnati, Ohio
3. Recent Experience and Present Status of Killed Virus Poliomyelitis Vaccine
   Joseph E. Smadel, National Institutes of Health, Bethesda, Maryland

FRIDAY, OCTOBER 26

Afternoon Panel Meeting

Therapy of Infections

Moderator: David E. Rogers

Division of Infectious Diseases, The New York Hospital-Cornell Medical Center, New York City

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Moderator: IRVING S. WRIGHT

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Moderator: MATHER CLEVELAND

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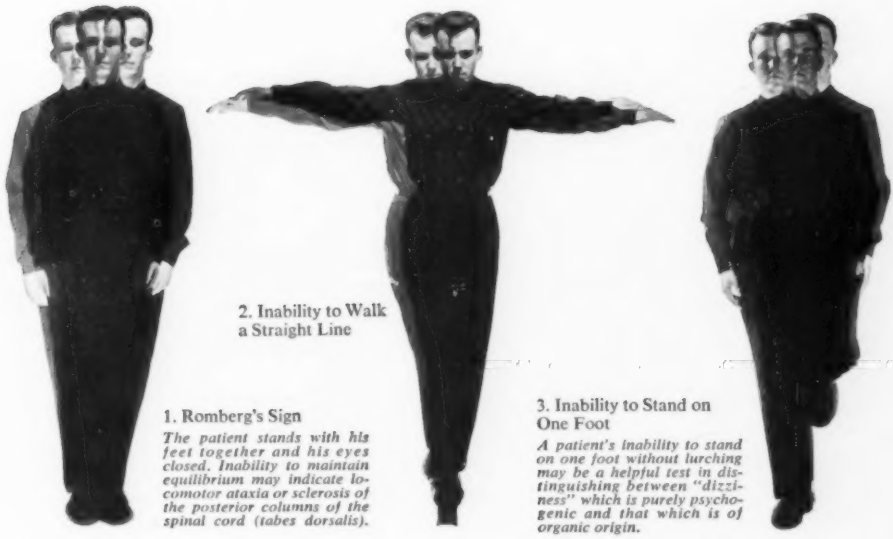
Notes on the Diagnosis and Management of "Dizziness"

II. False Dizziness



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1. Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

2. DeWeese, D. D.: Symposium: Medical Management of Dizziness. The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.

3. Kunkle, E. C.: Central Causes of Vertigo, J. South Carolina M. A. *50*:161 (June) 1954.

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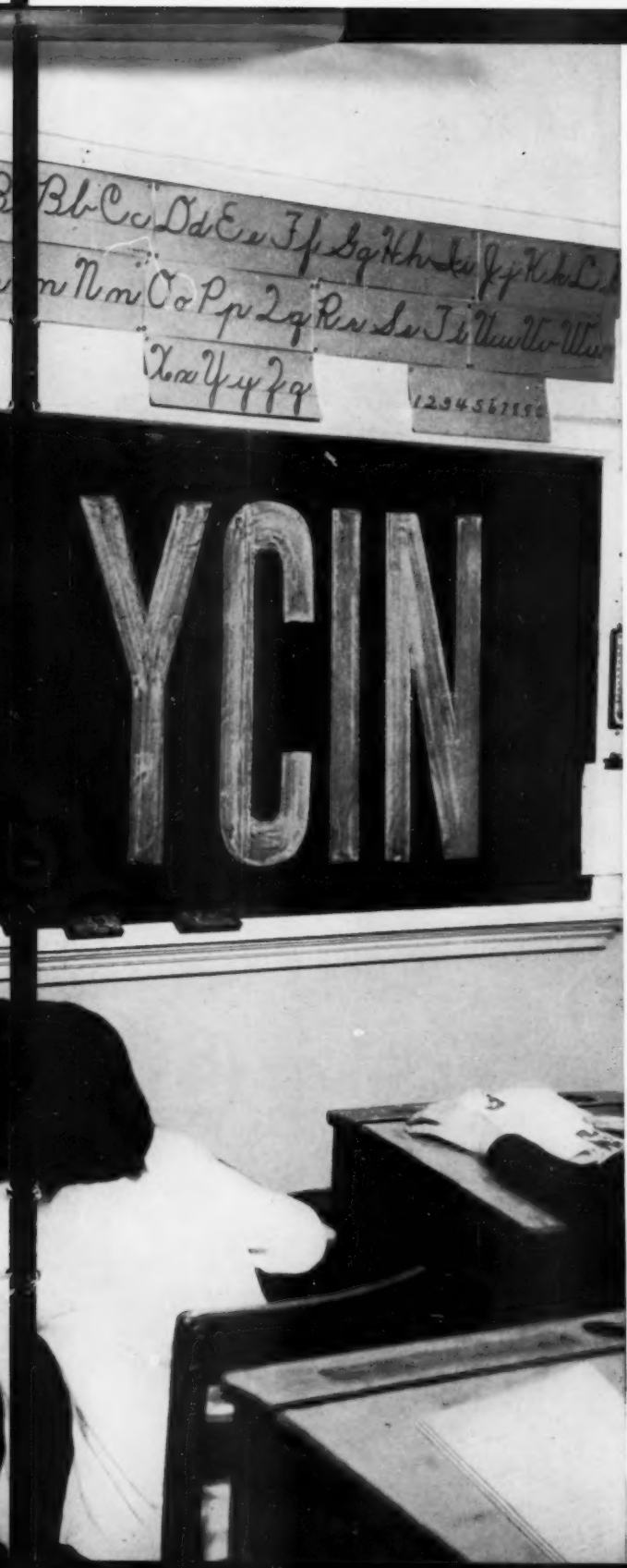

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[1]January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

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September 6 MANAGEMENT OF PROSTATIC OBSTRUCTION (part II—conclusion).

CANCER DETECTION BY AN INTERNIST—Richard R. McCormack, *Assistant Professor of Clinical Medicine, Cornell University Medical College, New York.*

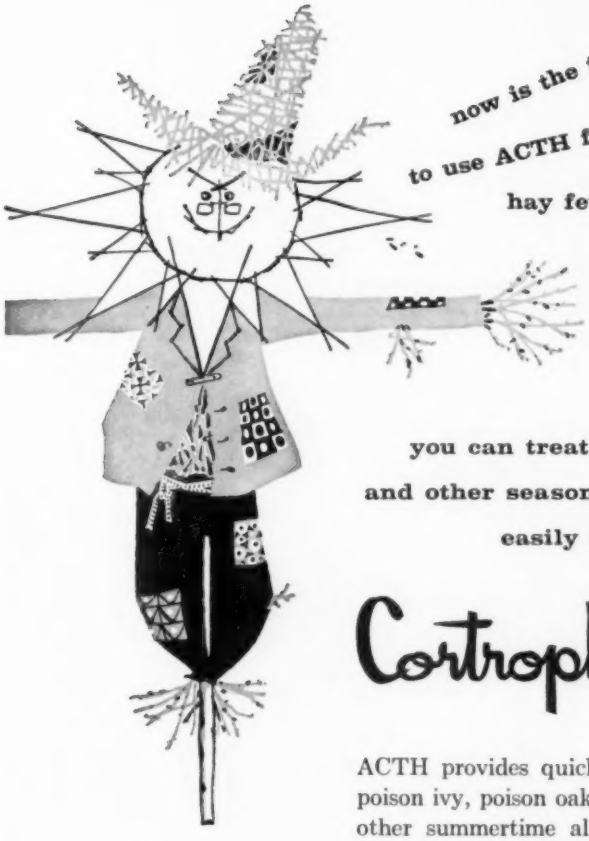
September 13 EXPERIMENTAL PROLONGATION OF THE LIFE SPAN—Clive M. McCay, Ph.D., *Professor of Nutrition, Cornell University, Ithaca, New York.*

HISTOPATHOLOGY OF THE PRECANCEROUS DERMATOSES—Arthur B. Hyman, *Associate Clinical Professor of Dermatology, New York University, New York.*

September 20 MEDICAL RESEARCH AND EDUCATION IN RELATION TO INDUSTRY—Willard C. Rappleye, *Dean, Faculty of Medicine, Columbia University, New York.*

THE ROLE OF INDUSTRY IN THE DISCOVERY AND MASS PRODUCTION OF ANTBIOTICS—John E. McKeen, *D. Eng., President, Chas. Pfizer & Co., Inc., Brooklyn, New York.*

September 27 MANAGEMENT OF CARDIOVASCULAR RENAL PROBLEMS IN THE AGED (panel)—Hugh Luckey, moderator, *Dean, Cornell University Medical College, New York, with* Mark D. Altschule, John E. Deitrick, Louis Leiter and Hugh Montgomery.



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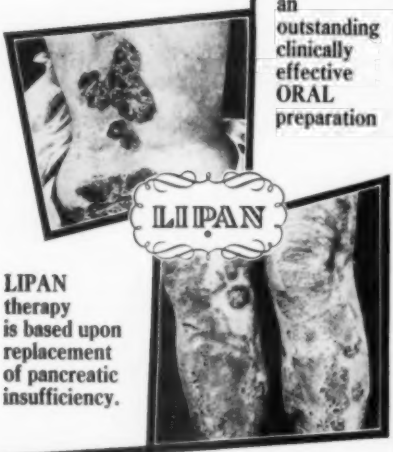

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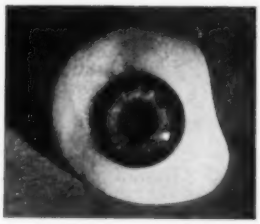

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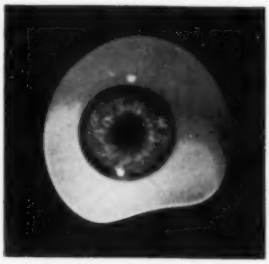

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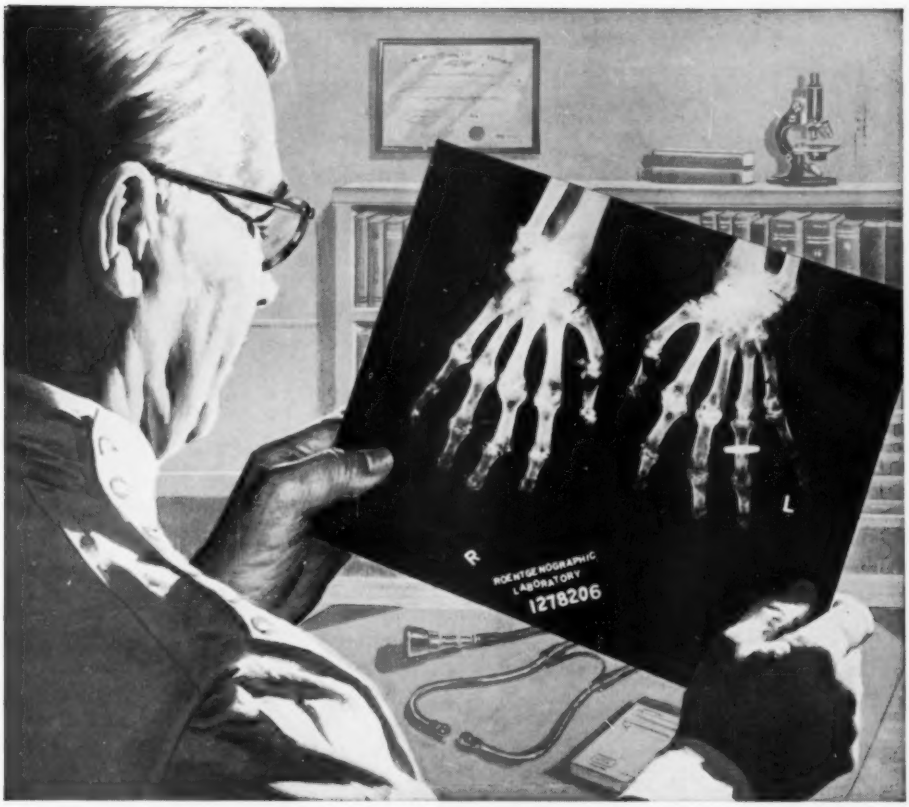

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REFERENCES:
1. J.A.M.A. 159:645 (Oct. 15) 1955.
2. J.A.M.A. 158:386 (June 4) 1955.

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1. Braceland, F.J.: Texas State J. Med. **51**:287 (June) 1955.
2. Lemere, F.: Northwest Med. **54**:1098 (Oct.) 1955.

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

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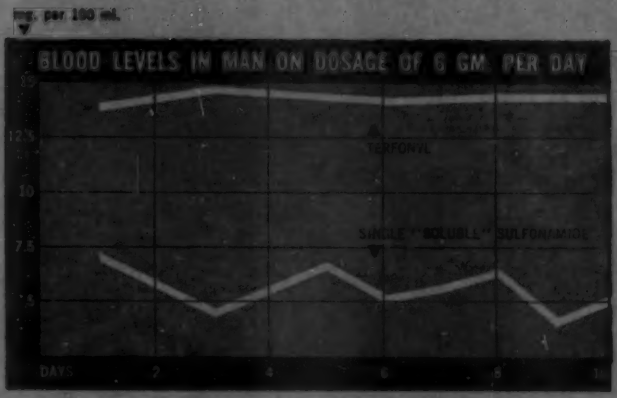

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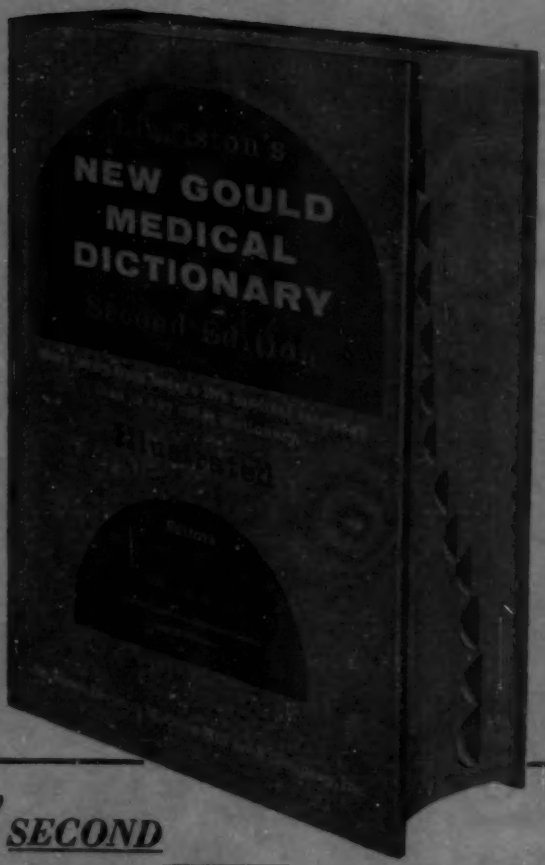

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